UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES ON OTTELIONE B, SYNTHESIS OF NOCARDIONE A, AND OXIDATIVE RADICAL CYCLIZATION

by

Stephen P. Fletcher

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Spring 2005

Library and Archives Canada

Published Heritage Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et Archives Canada

Direction du Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

0-494-08234-8

Your file *Votre référence*
ISBN:
Our file *Notre reference*
ISBN:

NOTICE:
The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:
L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

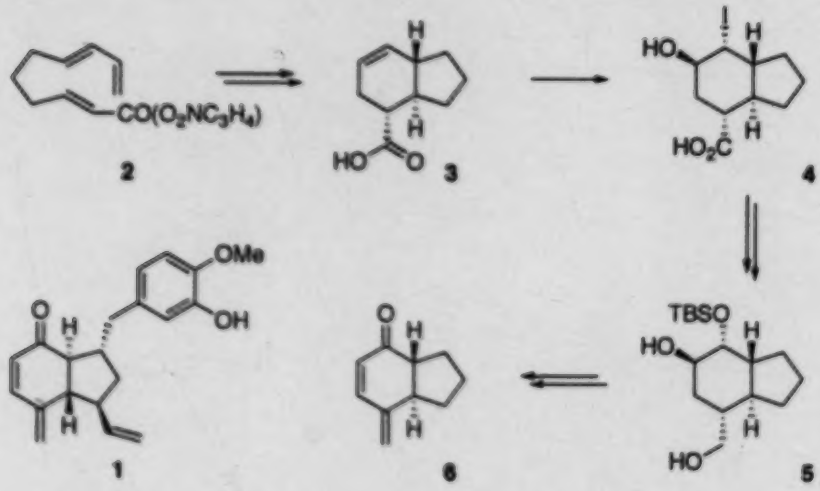
Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

Canada

To the Monks

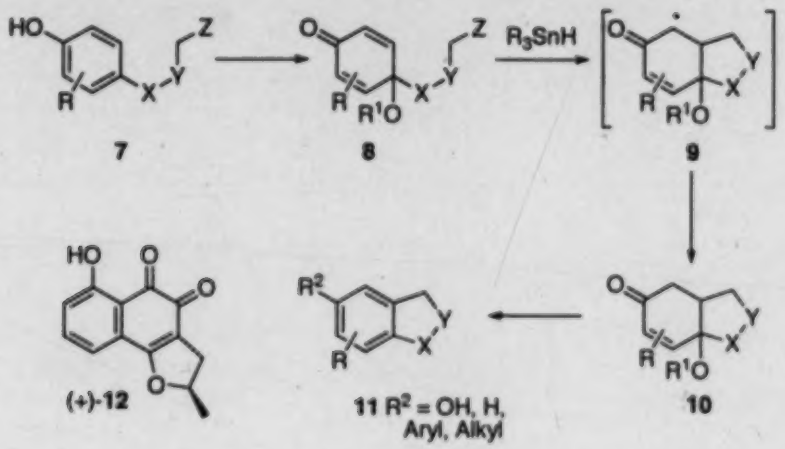
ABSTRACT

The first chapter of this thesis describes the synthesis of the dienone core (**6**) of the antitumor agent ottelione B (**1**) by two related routes. The ottelione dienone system inhibits tubulin polymerization, causing cell death, by a unique mechanism. The *trans* ring fused **3** was assembled by catalytic asymmetric intramolecular Diels-Alder cycloaddition of **2** and removal of the auxiliary. Compound **3** gave iodohydrin **4** when treated under standard iodolactonization conditions, and **4** was converted into **5**. Structures **3**, **4** and **5** were confirmed by single crystal X-ray analysis. Compound **5** was elaborated into *trans* dienone **6** by two related routes. The stereochemistry of the *trans* ring system was confirmed by degrading **6** to an earlier intermediate whose structure was established by X-ray analysis.



The final chapter of this thesis describes the development of a general indirect method for effecting radical cyclization onto a benzene ring. This process achieves the oxidative radical cyclization by converting a phenol (**7**) into a dienone (**8**), and then performing the radical cyclization (**8** → **9** → **10**) and rearomatization steps (**10** → **11**). The method forms five-, six-, and seven-membered heterocyclic rings fused to phenols (**11**, R^2 = OH). Modification allows both formation of non-phenolic products, and alkylation of the

intermediate **9**. The method is an effective route to oxygen heterocycles (X = O) and was applied to the synthesis of the enantiomer of a natural cell-cycle inhibitor [*ent*-nocardione A, (+)-**12**] in optically pure form. This procedure allowed a ten-fold overall yield increase over the other synthesis of optically pure **12**. The method is also a flexible and general route to benzo-fused nitrogen heterocycles **11** (X = NR). This application uses a cross-coupling strategy to synthesize the starting *p*-aminophenols containing an iodide (**7**, X = NR, Z = I). In the case of compounds **7** (X = NR), successful oxidation to **8** is dependant on the nature of the third nitrogen substituent (R) and suitable values for R were established.



ACKNOWLEDGMENTS

I would like to express my sincere gratitude to Dr. D. L. J. Clive for his support, encouragement, and advice during the course of my Ph.D. program, and for his assistance during the preparation of this thesis.

I would also like to thank my friends and colleagues for many helpful discussions, and for their support. In particular, I would like to acknowledge Dr. D. Coltart and Ms. S. Ardelean for their generous technical assistance during the initial stages of my laboratory work, and Dr. J. Wang for support throughout my program.

I gratefully acknowledge the financial assistance provided by the Natural Sciences and Engineering Research Council of Canada.

Lastly, I would like to offer a special thank you to my parents, and to my roommates for their constant support and encouragement.

TABLE OF CONTENTS

CHAPTER I
SYNTHESIS OF THE BICYCLIC DIENONE CORE OF THE ANTITUMOR AGENT OTTELIONE B

1	**INTRODUCTION**		2
1.1	*Tubulin and Microtubules*		2
	1.1.1	*Inhibition of Tubulin Polymerization in Microtubules*	2
	1.1.2	*Cytotoxic Agents that Inhibit Tubulin Polymerization Dynamics in Microtubules*	2
		(a) Inhibition of Polymerization Dynamics by Promotion of Microtubule Assembly	3
		(b) Inhibition of Polymerization Dynamics by Disruption of Microtubule Assembly	4
	1.1.3	*Inhibition of Microtubule Assembly by Alkylation of Critical Sulfhydryl Residues*	4
1.2	*The Otteliones*		7
	1.2.1	*Isolation and Biological Activity of Ottelione A (RPR112378), Ottelione B, and RPR115781*	7
	1.2.2	*On the Structure of the Otteliones*	8
	1.2.3	*Structural Features of the Otteliones*	9
	1.2.4	*Mechanism of Action of the Otteliones*	11
1.3	*Other Synthetic Work on the Otteliones*		12
	1.3.1	*A Route to Functionalized Hydrindenones Structurally Related to Ottelione A*	12
	1.3.2	*Model Studies on Structure 7.1 by Mehta and Reddy*	13
	1.3.3	*Model Studies on a Diastereomeric Core of Ottelione A by Mehta and Islam*	15
	1.3.4	*Synthesis of Two Epi-Otteliones by Mehta and Islam*	17
	1.3.5	*Total Synthesis of (±)-Otteliones A and B by Mehta and Islam*	21
	1.3.6	*Mehta and Islam's Enantioselective Synthesis of (+)- and (-)-Ottelione A and (+)- and (-)-Ottelione B*	23
	1.3.7	*Enantioselective Synthesis of (+)-Ottelione A, (-)-Ottelione B and (+)-3-Epi-Ottelione A by Araki et al.*	25

2	**Results and Discussion**		31
2.1	*Potential Synthetic Approaches to the Trans-Dienone Core*		31
2.2	*Synthesis of the Trans-Dienone Core*		32
	2.2.1	*Preparation of the Advanced Intermediate*	32
	2.2.2	*Attempted Elaboration to the Dienone Core*	35
	2.2.3	*Two Related Routes to the Dienone Core*	38
	2.2.4	*Proof of Stereochemistry of the Trans-Dienone Core*	43
3	**Conclusion**		45
4	**Future Research**		45
5	**Experimental**		47
6	**References and Footnotes**		63

Chapter 2

Formal Radical Cyclization onto a Benzene Ring: Formation of Benzo-Fused Oxygen Heterocycles, Synthesis of Nocardione A, and Formation of Benzo-Fused Nitrogen Heterocycles

1	**Introduction**		68
1.1	*Background*		68
	1.1.1	*Mechanistic Considerations*	68
	1.1.2	*Radical Cyclization onto Heteroaromatic Rings*	69
	1.1.3	*Attack on a Benzene Ring using Standard Radical Cyclization Conditions*	72
		(a) Formation of Polyaromatic Products	72
		(b) Examples of non-Polyaromatic Products	77
	1.1.4	*Application of the Xanthate method*	78
	1.1.5	*Cyclizations of Radicals from β-Dicarbonyl Compounds*	84
	1.1.6	*Samarium(II)-Initiated Cyclization onto an Aromatic Ring*	85
	1.1.7	*Radical Cyclization onto an Aromatic Ring without Rearomatization of the Ring*	86
	1.1.8	*Radical Attack on a Benzene Ring, followed by Ipso-Substitution*	87
2	**Results and Discussion**		88
2.1	*Research Objectives*		88
	2.1.1	*Development of a Generalized Approach to Radical Cyclization onto a Benzene Ring – An Indirect Method*	89
2.2	*Formation of Benzo-Fused Oxygen Heterocycles*		91

2.2.1 *Oxidation of p-Alkoxyphenols to Cross-Conjugated Ketones* 91
2.2.2 *Radical Cyclization of Cross-Conjugated Ketones and Rearomatization* 94
2.2.3 *Manipulation of the Radical Cyclization Products before Aromatization* 97
2.3 *Application to Natural Product Synthesis: Synthesis of Nocardione A* 99
2.3.1 *Cdc25 Phosphatases* 99
2.3.2 *Isolation and Biological Activity of Nocardione A* 101
2.3.3 *Previous Synthetic Work on the Nocardiones* 101
2.3.4 *Total Synthesis of Nocardione A* 104
2.4 *Formation of Benzo-Fused Nitrogen Heterocycles* 110
2.4.1 *Synthetic Considerations* 111
2.4.2 *Evaluation of Routes to p-Amino Phenols* 111
2.4.3 *The First Generation Approach* 115
(a) *Preparation of p-Amino Phenols* 115
(b) *Oxidation of p-Amino Phenols* 116
(c) *Radical Cyclization and Aromatization* 119
2.4.4 *Second Generation Approaches* 120
(a) *Cross-Coupling to Form Unprotected Aminoalkoxy-Phenols and Subsequent Manipulation* 121
(b) *Cross-Coupling of Primary Amides and Oxidation of Secondary p-Amidophenols* 124
(c) *Cross-Coupling of Protected Secondary Amino- and Amido-Alcohols and Subsequent Manipulation* 127
2.4.5 *Formation of Substituted Dihydroindoles* 130
2.4.6 *Manipulation of the Radical Cyclization Products before Aromatization* 135
3 **CONCLUSION** 137
4 **FUTURE RESEARCH** 138
4.1 *Formation of Benzo-Fused Oxygen Heterocycles* 138
4.2 *Application via ortho-Oxidation* 139
4.3 *Formation of Benzo-Fused Nitrogen Heterocycles* 140
4.4 *Application of the General Method to Compounds Requiring the Oxidation of a p-Alkylphenol* 145
4.4.1 *A Formal Method for meta-Alkylation* 145
4.4.2 *Synthesis of Benzo-Fused Carbocycles* 147

4.4.3 Synthesis of Benzo-Fused Medium Sized Ring 148
5 EXPERIMENTAL 151
6 REFERENCES AND FOOTNOTES 232

GENERAL CONCLUSION 239

LIST OF FIGURES

Figure 1	Single crystal X-ray analysis of (3a*S*,4*R*,6*R*,7*R*,7a*R*)-Octahydro-6-hydroxy-7-iodo-1*H*-indene-4-carboxylic Acid (**31.1**)	36
Figure 2	Single crystal X-ray analysis of (3a*R*,4*R*,7a*S*)-2,3,3a,4,5,7a-Hexahydro-1*H*-indene-4-carboxylic Acid (**28.5**)	37
Figure 3	Single crystal X-ray analysis of (3a*S*,4*R*,6*R*,7*R*,7a*R*)-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-octahydro-6-hydroxy-1*H*-indene-4-methanol (**35.5**)	40

List of Schemes

Chapter 1

Scheme 1 3
Scheme 2 5
Scheme 3 6
Scheme 4 6
Scheme 5 7
Scheme 6 8
Scheme 7 8
Scheme 8 10
Scheme 9 10
Scheme 10 13
Scheme 11 14
Scheme 12 16
Scheme 13 17
Scheme 14 18
Scheme 15 18
Scheme 16 19
Scheme 17 20
Scheme 18 21
Scheme 19 22
Scheme 20 23
Scheme 21 24
Scheme 22 25
Scheme 23 26

Scheme 24 27
Scheme 25 28
Scheme 26 29
Scheme 27 30
Scheme 28 33
Scheme 29 33
Scheme 30 34
Scheme 31 35
Scheme 32 36
Scheme 33 38
Scheme 34 39
Scheme 35 39
Scheme 36 41
Scheme 37 42
Scheme 38 43
Scheme 39 45
Scheme 40 46
Scheme 41 46
Scheme 42 47

CHAPTER 2

Scheme 1 68
Scheme 2 70
Scheme 3 70
Scheme 4 71
Scheme 5 71

Scheme 6 72
Scheme 7 73
Scheme 8 74
Scheme 9 75
Scheme 10 75
Scheme 11 76
Scheme 12 76
Scheme 13 77
Scheme 14 77
Scheme 15 78
Scheme 16 79
Scheme 17 80
Scheme 18 81
Scheme 19 81
Scheme 20 82
Scheme 21 82
Scheme 22 83
Scheme 23 83
Scheme 24 84
Scheme 25 85
Scheme 26 86
Scheme 27 86
Scheme 28 87
Scheme 29 87
Scheme 30 88
Scheme 31 89
Scheme 32 90

Scheme 33 90
Scheme 34 91
Scheme 35 92
Scheme 36 94
Scheme 37 95
Scheme 38 96
Scheme 39 96
Scheme 40 97
Scheme 41 98
Scheme 42 99
Scheme 43 102
Scheme 44 103
Scheme 45 105
Scheme 46 106
Scheme 47 107
Scheme 48 108
Scheme 49 108
Scheme 50 109
Scheme 51 112
Scheme 52 112
Scheme 53 113
Scheme 54 115
Scheme 55 116
Scheme 56 117
Scheme 57 118
Scheme 58 118
Scheme 59 119

Scheme 60 121
Scheme 61 122
Scheme 62 122
Scheme 63 123
Scheme 64 124
Scheme 65 125
Scheme 66 126
Scheme 67 127
Scheme 68 128
Scheme 69 129
Scheme 70 130
Scheme 71 131
Scheme 72 131
Scheme 73 132
Scheme 74 133
Scheme 75 134
Scheme 76 134
Scheme 77 136
Scheme 78 136
Scheme 79 139
Scheme 80 140
Scheme 81 141
Scheme 82 141
Scheme 83 142
Scheme 84 143
Scheme 85 144
Scheme 86 144

Scheme 87 145
Scheme 88 146
Scheme 89 147
Scheme 90 148
Scheme 91 148
Scheme 92 149
Scheme 93 150
Scheme 94 150
Scheme 95 151

List of Abbreviations

ABCN	1,1'-azobis(cyclohexanecarbonitrile)
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
9-BBN	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
t-Bu	*tert*-butyl
CAN	ammonium cerium(IV) nitrate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
Fm	9-fluorenylmethyl
Fmoc	9-fluorenylmethylcarbonyl
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
IBX	*o*-iodoxybenzoic acid
LAH	lithium aluminum hydride

LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
nM	nanomolar
PCC	pyridinium chlorochromate
Ph	phenyl
pM	picomolar
ppm	parts per million
SOMO	singly occupied molecular orbital
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TMS	trimethylsilyl
Tol	*p*-toluene-
TPP	tetraphenylporphyrin
Troc	trichloroethyl carbamate
Ts	*p*-toluenesulfonyl
TTMSS	tris(trimethylsilyl)silane

CHAPTER I

SYNTHESIS OF THE BICYCLIC DIENONE CORE OF THE ANTITUMOR AGENT OTTELIONE B

1 INTRODUCTION

1.1 Tubulin and Microtubules

1.1.1 Inhibition of Tubulin Polymerization in Microtubules

Microtubules are long, straight tubes found in a variety of eukaryotic cells. In equilibrium with a pool of tubulin monomers in the cytoplasm, microtubules rapidly assemble and disassemble in response to various stimuli. By changing the rate of tubulin polymerization, cells vary their shape and movement, and induce formation of various cellular processes.

Microtubule dynamics are involved in cell growth and division. During mitosis, the cytoskeletal microtubule network is dismantled and new microtubules are built that form the mitotic spindle. The importance of microtubules in mitosis makes them an attractive target for the development of compounds useful in cancer chemotherapy. It is likely that the dynamics of microtubules, and not just their presence, are critical for cell proliferation.[1]

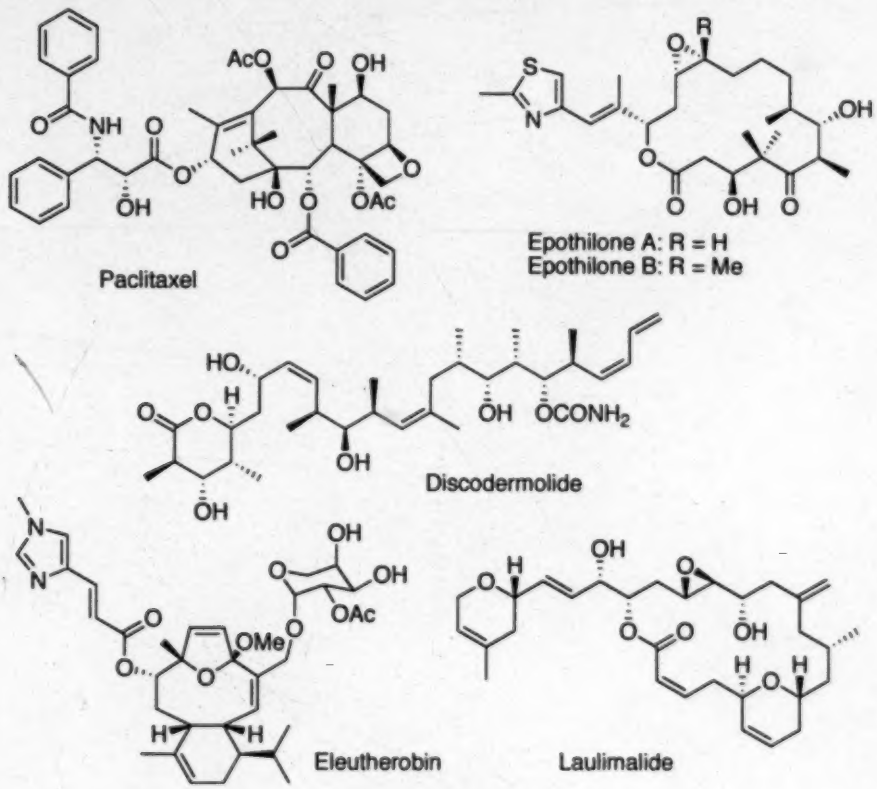
1.1.2 Cytotoxic Agents that Inhibit Tubulin Polymerization Dynamics in Microtubules

Tubulin-active agents cause the cells to arrest in a mitosis-like state, where the nuclear membrane has dissolved and reduplicated chromosomes have condensed. Such cells lack a functional spindle, fail to divide, and eventually undergo apoptosis.[2]

Antimitotic agents are traditionally thought to work by either promoting or inhibiting microtubule assembly.[3] It is not clear if the mechanisms of action of compounds that promote and those that inhibit assembly are fundamentally different, as at the lowest effective concentrations, both classes block microtubule dynamics and strongly increase the amount of time microtubules neither grow nor shorten, without modifying microtubule polymer mass.[4]

(a) Inhibition of Polymerization Dynamics by Promotion of Microtubule Assembly

Some agents cause the hyperassembly of tubulin, and stabilize the resultant microtubules, thereby disrupting microtubule dynamics. This class of drugs include paclitaxel[5] and the epothilones.[6] Other natural products such as discodermolide, eleutherobin, and laulimalide also work by this mechanism. These drugs only have a high affinity for tubulin in its polymer form, and drug-treated cells typically display increased microtubule density, and shorter microtubules organized into bundles.[2a]



Scheme 1

(b) Inhibition of Polymerization Dynamics by Disruption of Microtubule Assembly

The effect of drugs that inhibit microtubule assembly depends on the concentration of the drug. These effects range from complete disappearance of microtubules at higher concentration, to causing subtle defects in spindle function at lower concentrations.

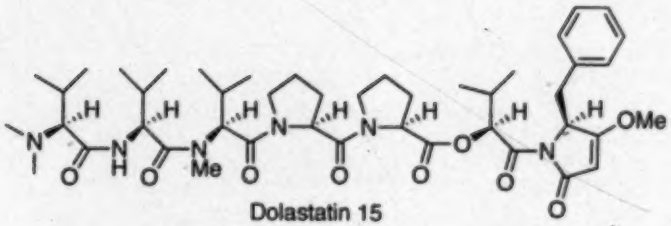
The natural product-derived agents that act through this mechanism either bind to β-tubulin at the *vinca* domain (named after the *vinca*-alkaloids),[7] or at the colchicine site. This binding to disassembled β-tubulin interferes with polymerization. Colchicine, because of its toxicity, is not used clinically for chemotherapy, but has served as a biological probe in the study of tubulin and microtubules.[8]

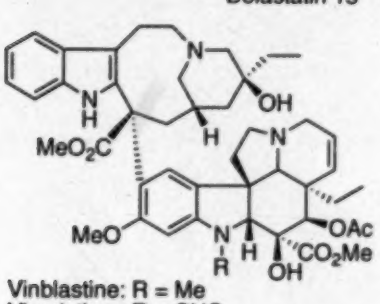
Vinblastine and vincristine (and their clinically approved derivatives) are *vinca* alkaloids that act at the *vinca* domain. These agents (see Scheme 2) competitively inhibit binding at the *vinca* domain, or they bind close to the *vinca* domain and act as noncompetitive inhibitors for the *vinca* site.[3] Inhibitory agents that act at the *vinca* domain include the ustiloxins, dolastatins, cryptophycins, and diazonamide A.[2]

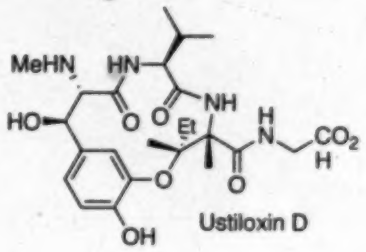
Many natural products bind to the colchicine site to inhibit microtubule assembly. These compounds are structurally simpler than those binding to the taxoid or vinca-alkaloid domain, and are exemplified by podophyllotoxin, stegnacin, and the combretastatins (Scheme 3). These, and many similar natural products, all have structural homology with either the trimethoxyphenol ring of colchicine, or the methoxytropolone moiety, or both.

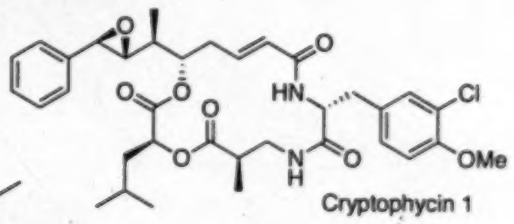
1.1.3 Inhibition of Microtubule Assembly by Alkylation of Critical Sulfhydryl Residues

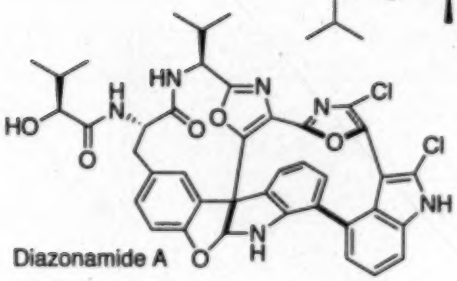
Tubulin has 20 sulfhydryl groups, and these are important in its ability to assemble. Compounds that alkylate cysteine residues define a third class of reagents that inhibit microtubule assembly. In 1974 it was shown that microtubule assembly can be inhibited completely by synthetic agents that react with sulfhydryl residues.[9] A large number of alkylating agents have been studied, but most compounds modify multiple cysteine residues.[10] Although it can also alkylate multiple cystine residues, 2,4-dichlorobenzyl











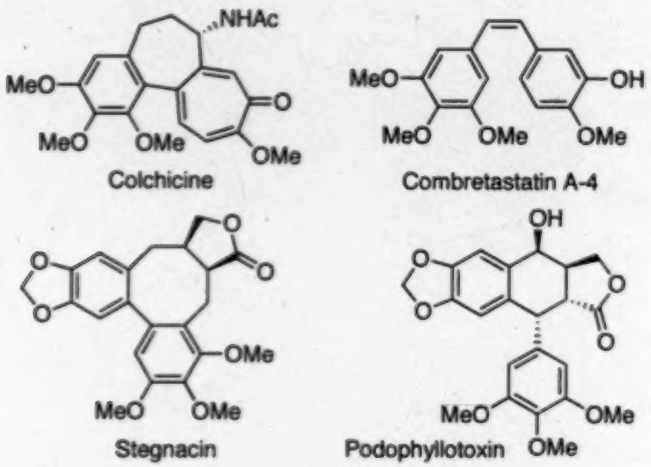
Scheme 2

thiocyanate reacts preferentially with Cys-239 of β-tubulin.[11]

Recently, two completely synthetic reagents, T138067,[12] and 4-*tert*-butyl-[3-(2-chloroethyl)ureido]benzene (4-*t*-BCEU, see Scheme 4)[13] were shown to react selectively with Cys-239 of β-tubulin and inhibit tubulin polymerization. Further, T138067 also inhibited colchicine binding to tubulin, and shows *in vivo* efficacy against multidrug-resistant tumors.

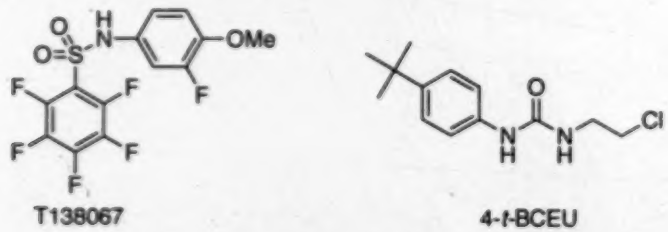
Although several clinically used anticancer agents affect microtubule dynamics,

tumor cells often develop resistance to these compounds faster than do normal cells. A recurring molecular pathway that leads to multidrug resistance in human cancers involves the enhanced expression of drug-efflux pumps. These efflux pumps recognize the relatively large, polycyclic microtubule inhibitors and stabilizers discussed above and actively remove them from tumor cells.[12]



Scheme 3

The selective covalent binding of T138067 to β-tubulin may explain how T138067 evades the cellular mechanisms of multidrug-resistant tumor lines. Thus, T138067 and other drugs that act by covalent binding to β-tubulin, may be useful for the treatment of human cancers that are resistant to standard chemotherapeutic agents.

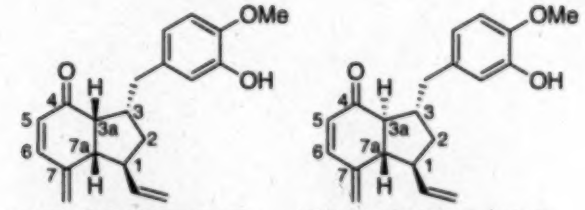


Scheme 4

1.2 The Otteliones

1.2.1 Isolation and Biological Activity of Ottelione A (RPR112378), Ottelione B, and RPR115781

Ottelia alismoides is a freshwater plant widely occurring in the rice fields and irrigation channels of Africa and southeast Asia. The otteliones, isolated from *O. alismoides*, have received much attention, as they exhibit remarkable and broad-ranging biological activity. In 1995, Chinese scientists, conducting clinical trials, found that *O. alismoides* extracts cured two cases of bilateral tuberculosis of the cervical lymph gland within three months.[14] Egyptian and American scientists (Hoye *et al.*) found that the crude cyclohexane extracts of *O. alismoides* collected from irrigation channels in the Nile Delta showed significant anticancer activity against cultured mouse tumor cell lines.[15] Hoye *et al.* isolated otteliones A (**5.1**) and B (**5.2**) in a 1:1 ratio in 0.0009% yield (dry weight).[15]



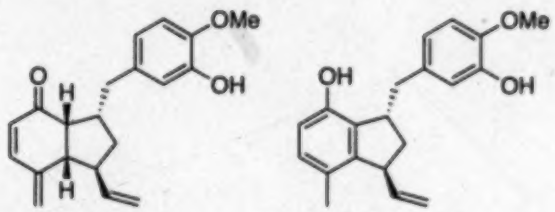
(+)-**5.1** (1*S*,3*S*,3a*S*,7a*S*) Ottelione A

(-)-**5.2** (1*S*,3*S*,3a*RS*,7a*S*) Ottelione B

Scheme 5

The otteliones were found to have conspicuously high antitumor activity, as judged by *in vitro* tests using a panel of human tumor cell lines. Against 60 human cancer cell lines tested at the National Cancer Institute in the US, both compounds reproducibly showed remarkable cytotoxicity. Ottelione A showed GI_{50} values of <100 pM and ottelione B of <1 nM for most cell lines, including a breast cancer (MDA-MB-435) cell line, and a CNS (SF-539) cancer cell line. Selective total growth inhibition was also observed in several cases.[15]

A French group at Rhône-Poulenc Rorer, also isolated two antitumoral substances from *O. alismoides*. One is ottelione A (**5.1**, RPR112378), and the other RPR115781 (**6.2**), a thermodynamically more stable aromatic tautomer.[15]



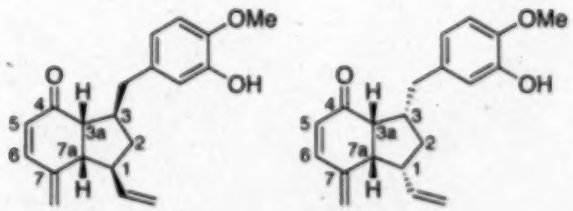
5.1 RPR112378 **6.2** RPR115781

Scheme 6

Relative to RPR115781 (**6.2**), ottelione A (**5.1**) was found to be much more cytotoxic, and had an IC_{50} of 0.02 nM for the human epidermoid KB cell line. It was also shown to inhibit a doxorubicin-resistant leukemia cell line (P388/DOX) with a GI_{50} of 3 nM. A detailed investigation of the anticancer mechanism revealed that ottelione A inhibits tubulin polymerization in microtubules (IC_{50} = 1.2 μM).

1.2.2 On the Structure of the Otteliones

In 1998, Hoye *et al.* employed high-field NMR spectroscopy and modeling studies to solve the structure of ottelione B (**5.2**).[15] Ottelione A (**5.1**) was at the time tentatively assigned structure **7.1**. The 1α,3α,3aα,7aα relative stereochemistry shown in **7.1** was



7.1 **7.2**

Scheme 7

judged[15] slightly more likely than the 1α,3α,3aβ,7aβ stereochemistry **7.2**.

Reinterpretation of the NMR data by the French scientists in 2000, led to the correct assignment of the 1α,3β,3aα,7aα (**5.1**) stereochemistry.[16]

The structural ambiguity surrounding ottelione A was solved by synthetic studies of Mehta *et al.*[17] aimed at **7.1** (the initially favored structure for ottelione A), and at **7.2**,[18] and finally, by the total synthesis of material identical to ottelione A (**5.1**).[19]

Neither group involved in the isolation of ottelione A report the specific rotation. The absolute stereochemistry remained uncertain until 2003 when nearly simultaneous total syntheses of (-)- and (+)- ottelione A and (-)- and (+)-ottelione B, by Mehta's group,[20] and (-)-ottelione A and (+)-ottelione B by Katoh *et al.*[21] established the absolute stereochemistry. According to Mehta and Islam,[20] Hoye's group (in unpublished work) arrived at the same conclusion by studies using the Mosher ester of a derivative of ottelione A.

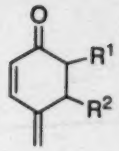
1.2.3 Structural Features of the Otteliones

Ottelione A and B possess a novel bicyclic hydrindane skeleton with four contiguous asymmetric centers. The compounds represent a rare compound class, and few examples of this structural type are known – apart from the otteliones themselves and compounds made in synthetic studies.

The 4-methylenecyclohex-2-enone (dienone) substructure **8.1** is rare and all groups involved in studies on the otteliones maintain that it is highly sensitive. As mentioned below, this unusual core selectively engages cysteine residues on tubulin, disrupting microtubule dynamics, and is partially responsible for the observed cytotoxicity.

Previously reported compounds having this substructure are limited to the hydrindene derivatives **9.1** and **9.2**, and the unsubstituted material **9.3**.

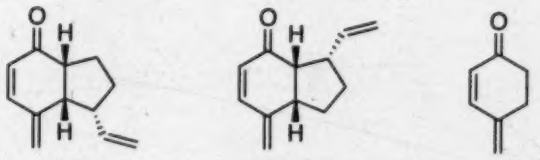
Although it may be expected that these dienones are quite sensitive to isomerization to their more stable aromatic (*p*-cresol) tautomers, **9.1** and **9.2** were prepared by pyrolysis at



8.1

Scheme 8

600 °C, and **9.3** was generated by 1 N sulfuric acid-catalyzed dehydration at 100 °C. The forcing conditions used suggest that these *cis* dienones may be kinetically protected from isomerization.



9.1 **9.2** **9.3**

Scheme 9

Ring fused dienones may be expected to undergo aromatization, and it is possible that an increased sensitivity of the *trans* isomer accounts for the isolation of **6.2** by the French group instead of ottelione B (**5.2**). It is noteworthy that Hoye *et al.* did not detect any *p*-cresol-like compounds in their crude plant extracts. The *trans* ring fused material also suffers the risk of epimerization of the stereogenic center α to the carbonyl, which would provide a *cis*-dienone. Although the relative stability of *cis* and *trans* isomers of hydrindanones is influenced by the substitution pattern[22] and can be changed by introduction of a double bond,[23] the situation with respect to ottelione B is not predictable by appeal to experimental evidence. In the case of ottelione B itself, the *trans* isomeric core may be stabilized by the orientation of the substituents of the natural product.

1.2.4 Mechanism of Action of the Otteliones

Ottelione A (RPR112378) is a very potent inhibitor of tubulin polymerization. It may have a mechanism of action similar to T138067; both inhibit colchicine binding, but not vinblastine binding. It was determined that ottelione A (**5.1**), like T138067, binds covalently and specifically to Cys-239. In contrast, RPR115781 (**6.2**) is a less active and reversible tubulin-binding drug.[2] These properties make the otteliones valuable lead compounds for design of new tubulin inhibitors.

It has been proposed that the otteliones can act sub-stoichiometrically because drug-tubulin complexes are incorporated into growing microtubules, blocking further tubulin addition.[10] The chemical structure of the otteliones suggests the potential for alkylating tubulin residues, where the dienone moiety could be attacked by sulfhydryl groups. When ottelione A was incubated with sulfhydryl-rich molecules – presumably preventing its interaction with tubulin sulfhydryl groups – a partial loss of activity was observed. The residual activity of ottelione A after incubation is presumably due to the fact that the benzene ring is able to interact with tubulin.[10] The benzene ring, which is substituted with methoxy and hydroxyl groups, is vaguely similar to the tropolone ring of colchicine, and may bind to the tropolone subsite for colchicines. RPR115781, which contains the same benzene ring, but not the dienone moiety, was found to prevent colchicine binding at high concentrations.[10]

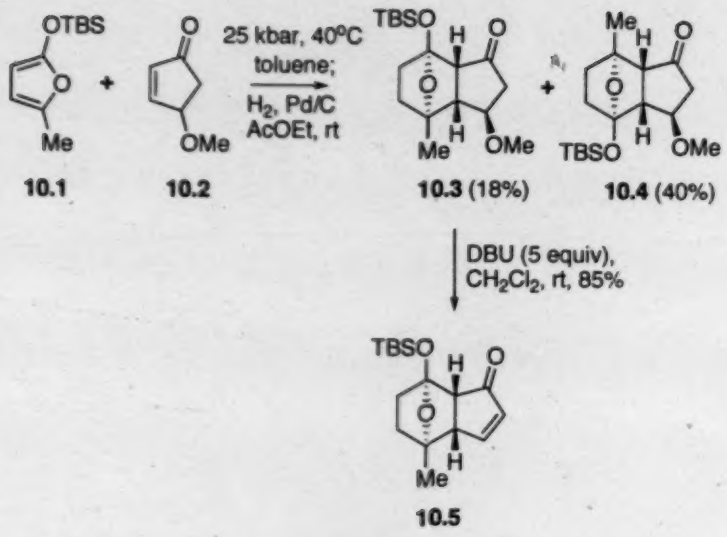
Ottelione A (RPR112378, **5.1**) and RPR115781 (**6.2**) are cytotoxic and arrest the cell cycle. However, ottelione A is 10,000 times more cytotoxic than **6.2** against the human epidermoid KB cell line, whereas it is only 5-fold more active against tubulin. The simplest interpretation of these results is that ottelione A may have better cell retention because of alkylation with sulfhydryl groups of tubulin or other proteins. This proposed mechanism of action is reminiscent of the reasoning used to describe the evasion of the cellular mechanisms of multidrug-resistant tumor lines by T138067.[10]

1.3 Other Synthetic Work on the Otteliones

When we began our synthetic work, a model study on a possible route to the structure then thought to represent ottelione A had been published by Mehta and Reddy.[17] During the course of our work, model studies on a route to another possible formulation of ottelione A were reported by Mehta and Islam,[18] as was a route to functionalized hydrindenones by Trembleau *et al.*[24] Immediately after our work, the total synthesis of (±)-ottelione A, and its ready conversion to (±)-ottelione B, was reported by Mehta and Islam.[19] Mehta and Islam have recently described their earlier work on the synthesis of two *epi*-ottelione derivatives,[25] and the enantioselective total syntheses of (+)- and (-)-ottelione A and (+)- and (-)-ottelione B, establishing the absolute configuration of the natural products.[20] Araki *et al.* have recently published the enantioselective total synthesis and absolute configuration of otteliones A and B,[21] and an enantioselective synthesis of 3-*epi*-ottelione A.[26]

1.3.1 A Route to Functionalized Hydrindenones Structurally Related to Ottelione A

A Diels-Alder cycloaddition approach to functionalized hydrindenones related to ottelione A was reported in 2000. The products are *cis* fused.[24] Cycloaddition of furan **10.1** to 4-methoxycyclopent-2-enone was found to take place with a regioselectivity opposed to that predicted by FMO theory, so that the yield of desired **10.3** was only 18%. This regioselectivity was the result of a thermodynamically controlled cycloaddition. However, the highly functionalized hydrindanone **10.3**, upon exposure to DBU, provided **10.5**. This contains an enone system that could, in principle, be used to introduce the substituents of the five membered ring of ottelione A. Presumably, the enone moiety of the natural product would then be generated through a sequence involving cleavage of the tetrahydrofuran ring.



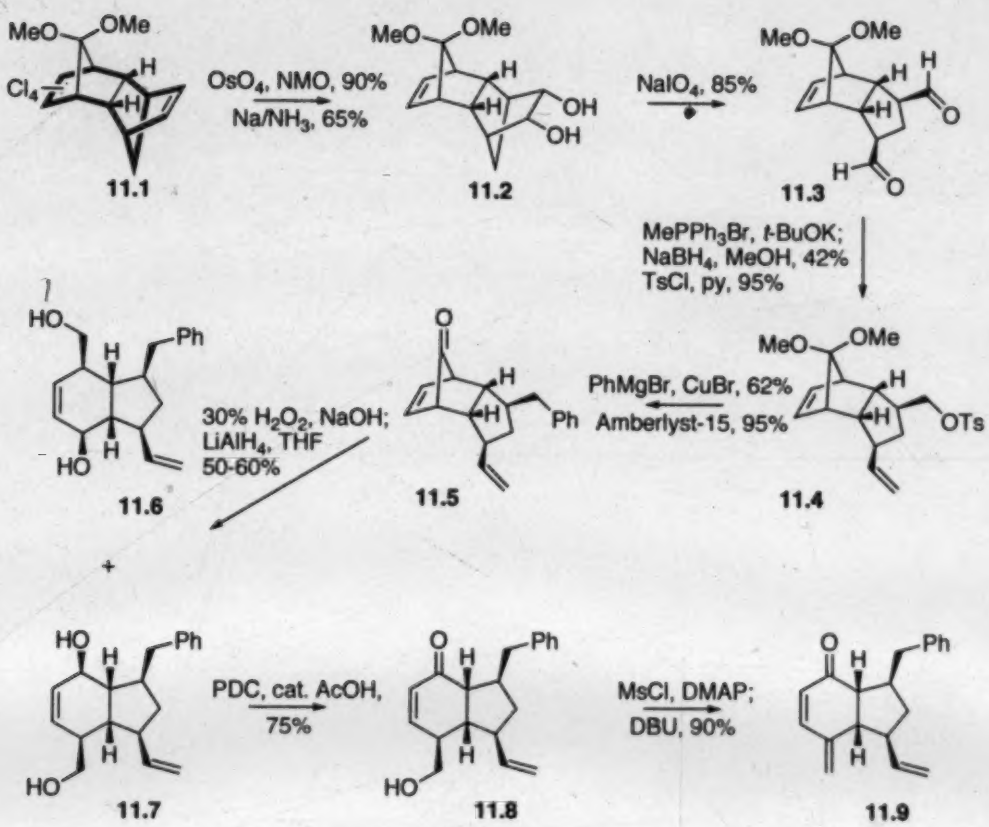
Scheme 10

1.3.2 Model Studies on Structure 7.1 by Mehta and Reddy

Mehta and Reddy reported the first synthesis of an actual ottelione framework in 1999.[17] At that time formula **7.1** was favored for ottelione A. Their approach is short and stereoselective but not regioselective.

The strategy relies on polycyclic compound **11.1** as the starting point. The bicyclic hydrindane framework and all four stereogenic centers present in **7.1** are embedded in **11.1** (see the bold lines in **11.1**, Scheme 11). The task is then to disengage the desired bicyclic skeleton from the polycycle while preserving the stereochemical features.

An inverse electron-demand Diels-Alder reaction between tetrachloro-5,5-dimethoxycyclopentadiene and norbornadiene provided **11.1** (93%). Regioselective dihydroxylation of the unsubstituted double bond, followed by dehalogenation, gave diol **11.2**. Oxidative cleavage was then used to break a bridging carbon-carbon bond and release in a completely stereocontrolled manner what would become the two sidearms of **7.1**. Desymmetrization of compound **11.3** was accomplished by a carefully controlled mono-Wittig olefination and reduction sequence, followed by tosylation to give **11.4**. Copper



Scheme 11

mediated cross coupling of **11.4** with PhMgBr and then acetal deprotection led to **11.5**.

The key Baeyer-Villiger oxidation/ring-opening sequence, used to extract the hydrindane framework from the bridged system, gave two regioisomeric alcohols **11.7** and **11.6** (55:45) in 50-60% yield. As this process is not selective, this carbon-carbon bond breaking approach to the six-membered ring of ottelione A was abandoned in more advanced studies, although the sidearms of the natural product on the five-membered ring continued to be generated in this manner in Mehta's further work (see below).

The sequence to **11.9** was completed by oxidation of **11.7**, and DBU mediated elimination of a mesylate. A regioisomer of **11.9** (where the benzyl and vinyl moieties are interchanged) was also generated from **11.6**, using a similar approach. It is possible that

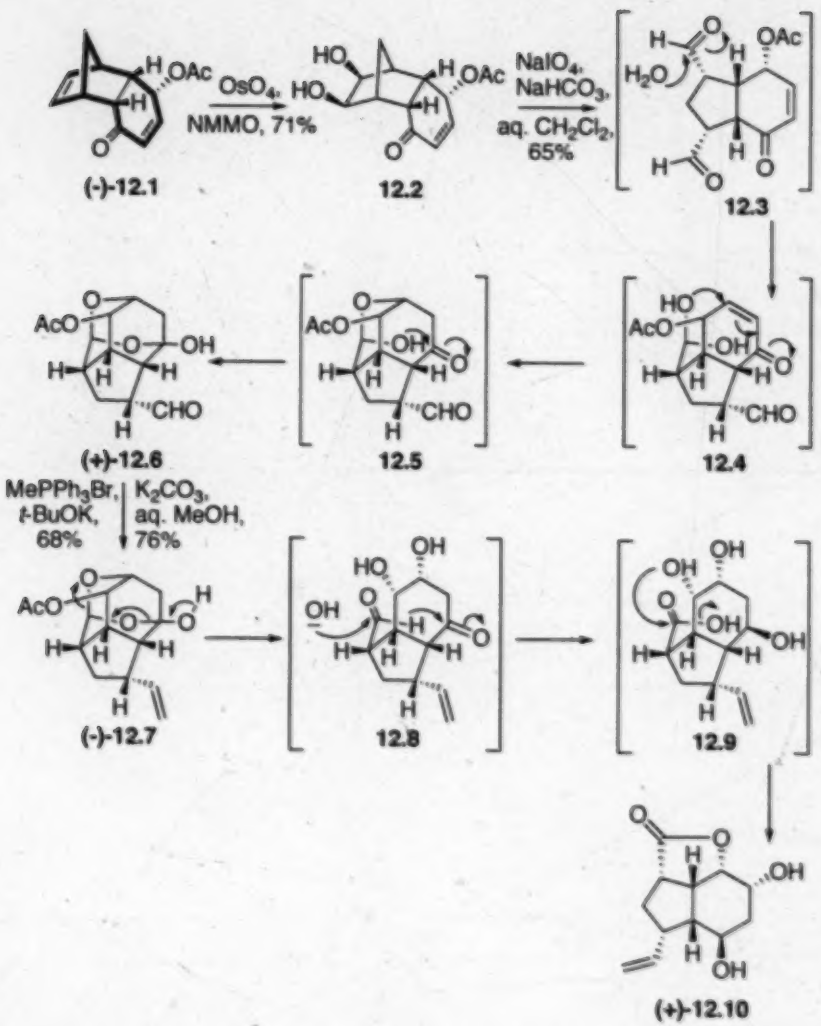
compound **11.9** is spectroscopically different enough from ottelione A to have indicated to Mehta and Reddy that the core could not have this relative stereochemistry, and Mehta next published an approach toward **7.2**, the then less favored formulation for ottelione A.

1.3.3 Model Studies on a Diastereomeric Core of Ottelione A by Mehta and Islam

Mehta's strategy toward diastereomeric structure **7.2** for ottelione A is reminiscent of the above work. The *cis*-hydrindane framework and the four desired stereogenic centers are present in tricycle **12.1** (see the bold lines in **12.1**, Scheme 13). In this case, extracting the hydrindane moiety was eventful, and seems highly fortuitous. This short sequence represents an enantio-, regio- and stereoselective route to the **7.2** framework.[18]

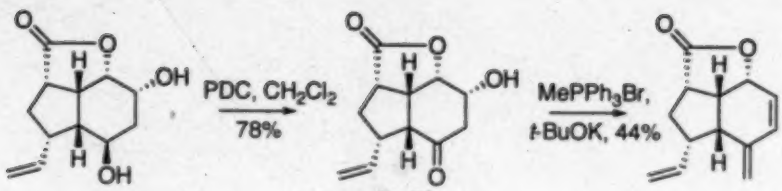
Compound **12.1**, derived by Diels-Alder reaction, was resolved enzymatically, and (-)-**12.1** underwent chemoselective dihydroxylation [(-)-**12.1** → **12.2**]. Brief exposure to periodate caused oxidative diol cleavage (Scheme 12). This process did not give the expected dialdehyde, but instead a tetracyclic product (+)-**12.6**. This was formed through a cascade of intramolecular cyclizations, beginning with hydration of **12.3**, followed by intramolecular Michael addition to the enone moiety in **12.4**, so as to produce **12.5**. Further intramolecular acetalization generated the tetracyclic dioxamantanoid framework of (+)-**12.6**. Through what would appear to be remarkable good luck, three functionalities, an aldehyde, an olefin and a ketone were internally protected, so that the free aldehyde group in (+)-**12.6** could be manipulated selectively. Wittig olefination then gave (-)-**12.7**. Again, an interesting series of events followed brief exposure of (-)-**12.7** to base. Acetal opening and deacylation led to keto-aldehyde **12.8**, which underwent an intramolecular Cannizzaro reaction (**12.8** → **12.9**). The resulting trihydroxy acid cyclized to give lactone (+)-**12.10**.

Conversion of (+)-**12.10** to **13.2** (Scheme 13) was accomplished by regioselective oxidation. Wittig methylenation of **13.2** resulted in both olefination and spontaneous dehydration to the core diene moiety. Mehta's model study, stops at diene **13.3**,



Scheme 12

although, as his next publication deals with the revised structure **5.1**, he may actually have converted **13.3** to a more advanced material, but not described this work in his publications. Compound **18.6** (see Scheme 18), which is a diastereomer of **13.3**, was advanced to the natural product so that the transformation of **13.3** → **7.2** (now known to be the incorrect structure) should have been possible.



12.10 **13.2** **13.3**

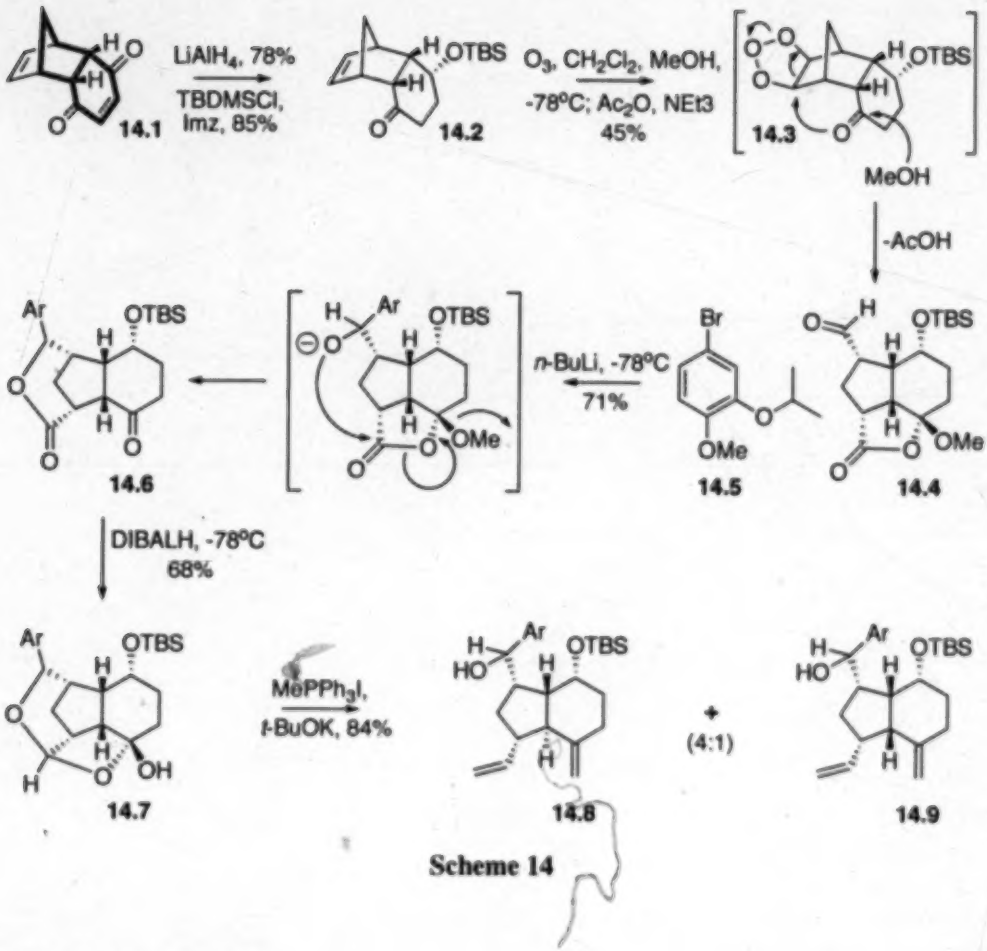
Scheme 13

1.3.4 Synthesis of Two Epi-Otteliones by Mehta and Islam

The work discussed in this section, which represents routes to **7.1** and **7.2**, was reported after the total syntheses of otteliones A and B, but is the research that established **5.1** as the correct structure of the ottelione A.[23]

The route begins (Scheme 14) with **14.2**, where the enone functionality of **12.1** has been replaced by a saturated ketone and the alcohol is protected as a silyl ether (*cf.* Scheme 12, **12.1**). The close proximity of the ketone to the double bond undergoing ozonolysis (**14.2** → **14.3** → **14.4**), leads to unsymmetrical cleavage under the conditions used, and formation of **14.4** (45%) was regioselective, due to the assisted intramolecular cleavage of the molozonide **14.3**. Addition of the organolithium reagent derived from **14.5**, was chemoselective for the aldehyde, providing **14.6** as a single diastereomer. Reduction of the lactone moiety was also achieved chemoselectively, and gave **14.7** with two internally masked carbonyl groups.

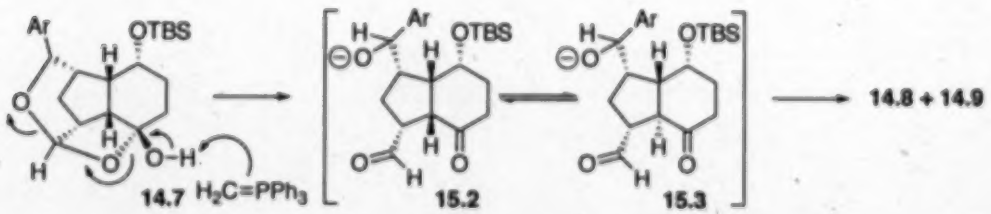
Global Wittig olefination installed the vinyl and terminal methylene groups and provided diastereomeric diolefins **14.8** and **14.9**, with the *trans*-isomer predominating by a 4:1 ratio. This major product is formed by ylide-mediated bis-acetal opening in **14.7**, leading to a ketone (Scheme 15, **14.7** → **15.2**), which undergoes bridgehead isomerization before olefination (**15.2** → **15.3**), giving **14.8**. It is noteworthy that the stereochemistry of the *endo*-aldehyde intermediates **15.2** and **15.3** (Scheme 15) remained secure during the Wittig reaction. This may be due to partial acetal character that stabilizes the aldehyde



Scheme 14

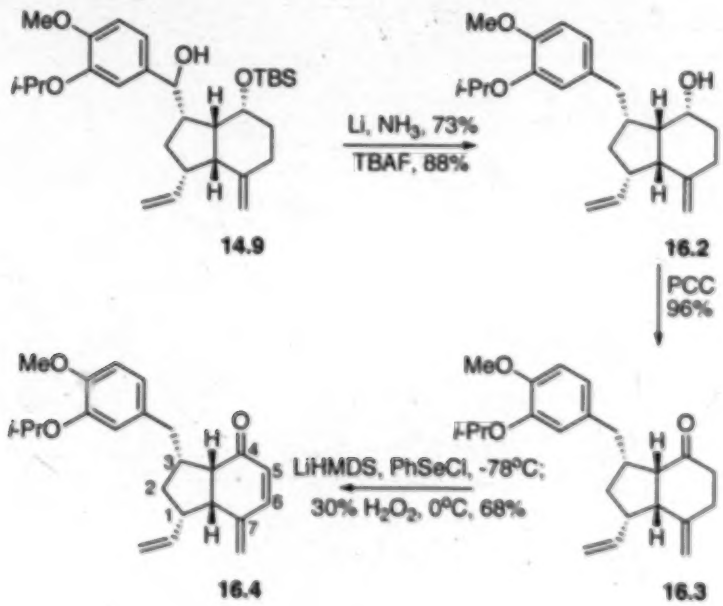
before Wittig olefination.

The minor product **14.9**, which had maintained its stereochemical integrity during the Wittig reaction, was elaborated to ottelione derivative **16.4** by reductive deoxygenation



Scheme 15

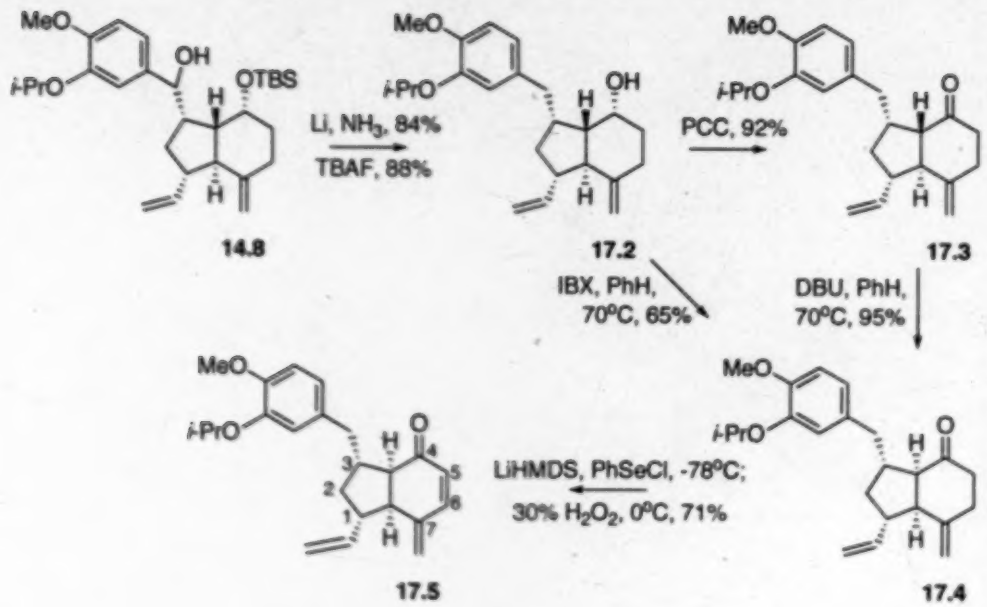
of the benzylic hydroxyl group and desilylation (**14.9** → **16.2**, Scheme 16), oxidation to ketone **16.3**, and finally generation of the 4-methylenecyclohex-2-enone substructure by a phenylselenation-selenoxide elimination sequence (**16.3** → **16.4**). Analysis of the NMR spectra of **16.4** revealed spectral features distinctly different from natural ottelione A, and it was decided that **16.4** most likely represents a 1-*epi*-ottelione A structure.



Scheme 16

Trans-hydrindane **14.8**, the major Wittig product (see Scheme 14), was elaborated to the 3-*epi*-ottelione derivative **17.5** (Scheme 17), through a reaction sequence involving another unanticipated epimerization. Deoxygenation and deprotection provided *trans*-alcohol **17.2**, whose structure was confirmed through X-ray crystal analysis of its *p*-nitrobenzoate. After PCC oxidation to **17.3**, exposure to base afforded **17.4**, as did direct oxidation of **17.2** with IBX, a reagent known[27] to promote epimerization.

It is interesting to note that during the formation of **14.7**, epimerization of a *cis*-hydrindane to the *trans*-hydrindane **14.8**, was observed, while in the case of *trans*-



Scheme 17

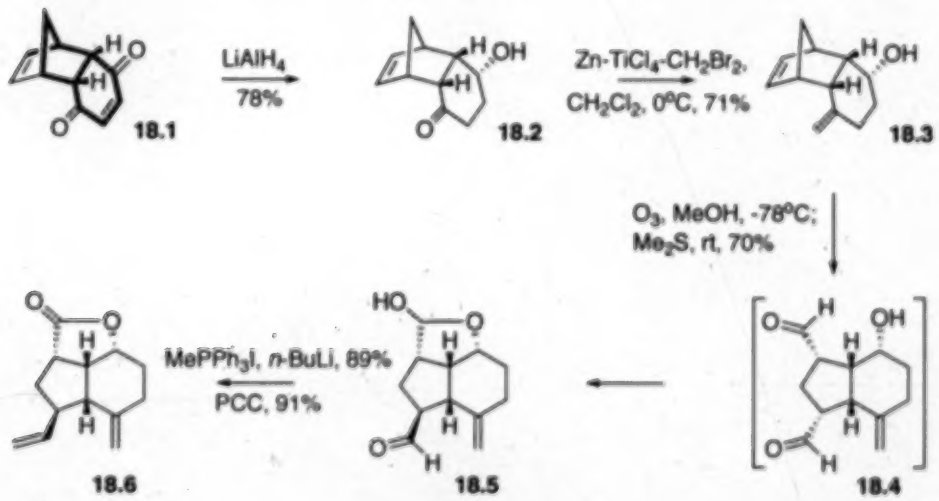
hydrindane **17.3**, epimerization to the *cis* isomer **17.4** occurred. Mehta calculated the heats of formation (AM1 level) for **17.3** and **17.4**, and the results indicated that **17.4** was about 7 Kcal/mol more stable than **17.3**. It appears that reallocation of groups and the carbonyl moiety (*cf.* **15.2** and **17.3**) on the hydrindane framework can profoundly affect the *cis vs trans* isomer stability. Interestingly, in elaborating *cis*-**14.7** to *cis*-**17.4**, both the hydrindane ring junctions had been sequentially inverted.

Formation of **17.4** was a desirable outcome as the stereochemistry at the four stereogenic centers corresponds to that present in the then-favored structure (**7.1**) of ottelione A. Thus, **17.4** was subjected to the phenylselenation-selenoxide oxidation sequence to give **17.5**. The NMR data of **17.5** was again not consistent with **7.1**, which implied the need for revision of the stereochemistry of the natural product. This revision was made by reinterpretation of the spectral data, and through the synthesis described below.

1.3.5 Total Synthesis of (±)-Otteliones A and B by Mehta and Islam

Mehta and Islam's total synthesis of racemic ottelione A, like the earlier model studies, relies on an extractable *cis*-hydrindane framework (see the bold lines in **18.1**) embedded in a readily available starting polycyclic compound.[19] In a manner similar to the above work, the functional groups in **18.1** were elaborated in a regio- and stereoselective manner to the substitution and functionalization pattern of the natural product. This work however required an epimerization to change the stereochemistry of a side arm liberated from the original bicycle.

Bicycle **18.2**, readily available through partial reduction of the Diels-Alder adduct of cyclopentadiene and benzoquinone (**18.1**), was subjected to Lombardo methylenation (**18.2** → **18.3**, Scheme 18). Careful ozonolytic cleavage (**18.3** → **18.4**) then produced two carbonyl moieties, as only the strained cyclic olefin reacts. The resulting aldehyde **18.5** originates from (a) intramolecular protection of one of the aldehyde groups of **18.4** by a well-positioned α-hydroxyl, and (b) the desired concomitant epimerization of the second aldehyde to the thermodynamically more stable *exo* conformation. (*cf.* Scheme 14, **14.7** →

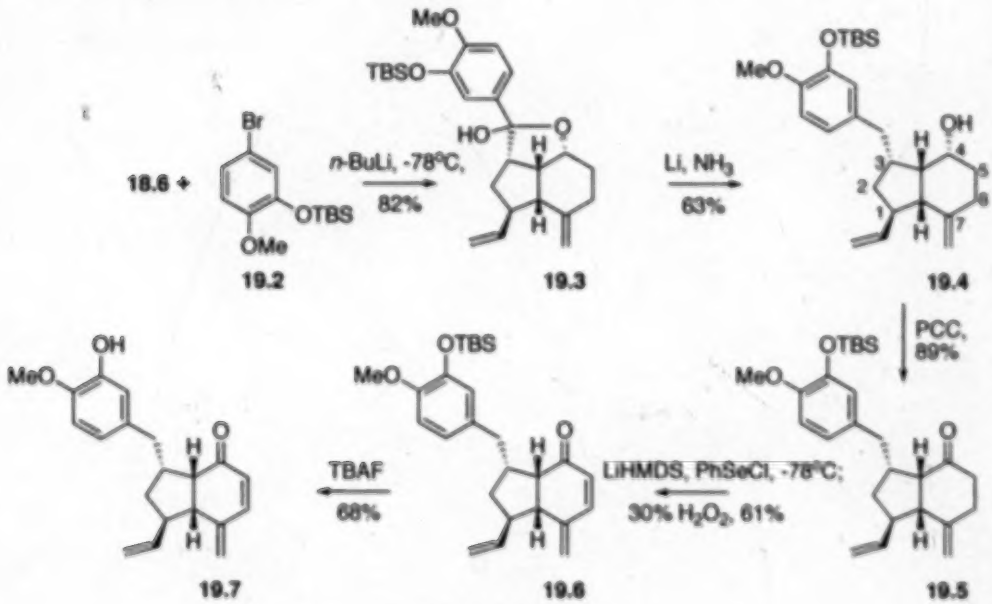


Scheme 18

14.8, Scheme 15, **15.2** → **15.3** where no epimerization of the aldehyde occurred).

It is noteworthy that this synthetic route does not involve an enone (*cf.* Scheme 12, **12.2** → **12.6**), or ketone functionality (*cf.* Scheme 14, **14.2** → **14.3** → **14.4**), so that the formation of polycyclic products, which arise through intramolecular cascade reactions during ozonolysis, is avoided.

With the regio- and stereochemistry of **18.5** set up for elaboration to the revised structure for ottelione A, the synthesis continued with Wittig olefination to install the vinyl side chain, and oxidation of the lactol moiety to **18.6**. This structure was confirmed through single crystal X-ray analysis.



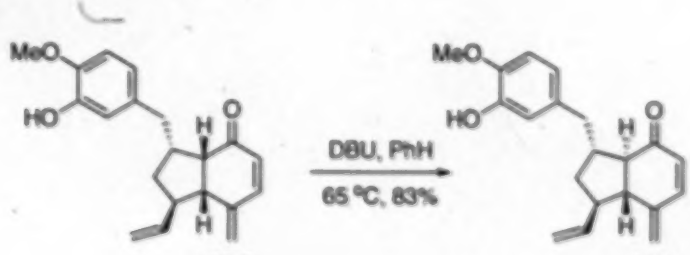
Scheme 19

Introduction of the benzylic side chain (Scheme 19) was accomplished by addition of an organolithium reagent derived from **19.2** (**18.6** → **19.3**) and deoxygenation to **19.4**, which liberates the C-4 hydroxyl group on ring A. The *cis*-fused dienone moiety was

produced through oxidation to **19.5**, and regioselective phenylselenation, followed by selenoxide elimination to **19.6**.

If **19.5** was susceptible to epimerization (*cf.* **14.7** → **14.8**, Scheme 14, **17.3** → **17.4**, Scheme 17) this fact was not mentioned by Mehta and Islam.

Fluoride mediated deprotection of **19.6** provided racemic ottelione A (**19.7**), whose spectroscopic data matched those of the natural product. This route represents an 11-step regio- and stereochemically controlled synthesis of ottelione A in 5.4% overall yield, which establishes the structure of the natural product. The authors also report that synthetic ottelione A undergoes smooth epimerization to ottelione B (83%, see Scheme 20) on exposure to DBU. The NMR spectra of synthetic ottelione B were used to confirm the structure of the natural product.



19.7 **20.2**

Scheme 20

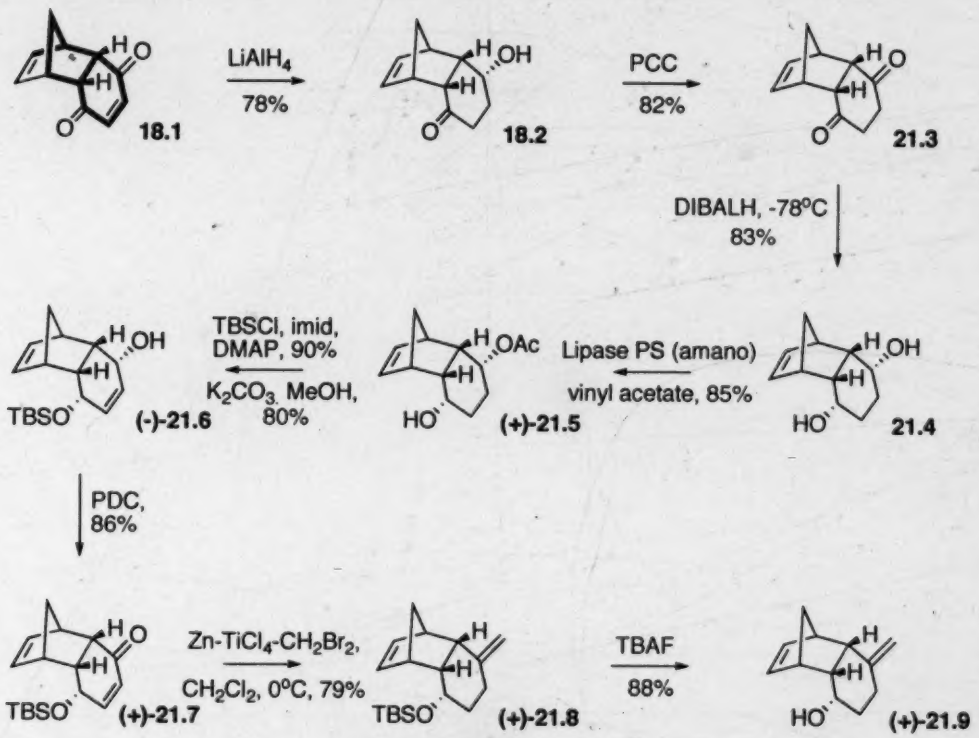
The claimed smoothness of the conversion of **19.7** to **20.2** has been thrown in doubt by the recent enantioselective total synthesis of ottelione A and B by Araki *et al.* (see Section 1.3.7).

1.3.6 Mehta and Islam's Enantioselective Synthesis of (+)- and (-)- Ottelione A and (+)- and (-)- Ottelione B

The enantioselective syntheses reported by Mehta and Islam were the first to establish the absolute configuration, and to provide values for the specific rotations, which

were not mentioned in either of the isolation papers. According to Mehta, Hoye *et al.* found ottelione A has a rotation of +14 (*c* 0.87, $CDCl_3$), and ottelione B a rotation of -276 (*c* 2.0, $CHCl_3$). The French group, in contrast, found that ottelione A has the opposite rotation, -20.8 (*c* 0.5, CH_2Cl_2). Mehta's work established the absolute configuration of ottelione A (+)-**5.1** and ottelione B as (-)-**5.2** (Scheme 5).[20]

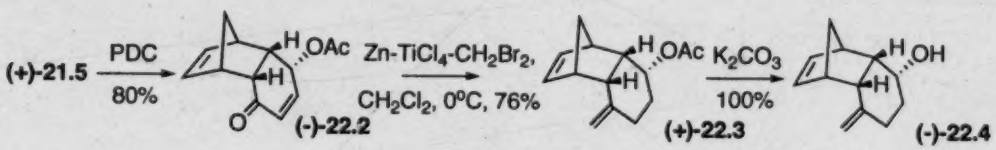
The above racemic synthesis began with Diels-Alder adduct **18.1**, and used racemic **18.2** as a key intermediate. The optically pure syntheses begin with olefin (+)-**21.9**



Scheme 21

(Scheme 21) or (-)-**22.4** (Scheme 22), where either enantiomer was elaborated to the optically pure natural products, following essentially the same route as used in the racemic synthesis.

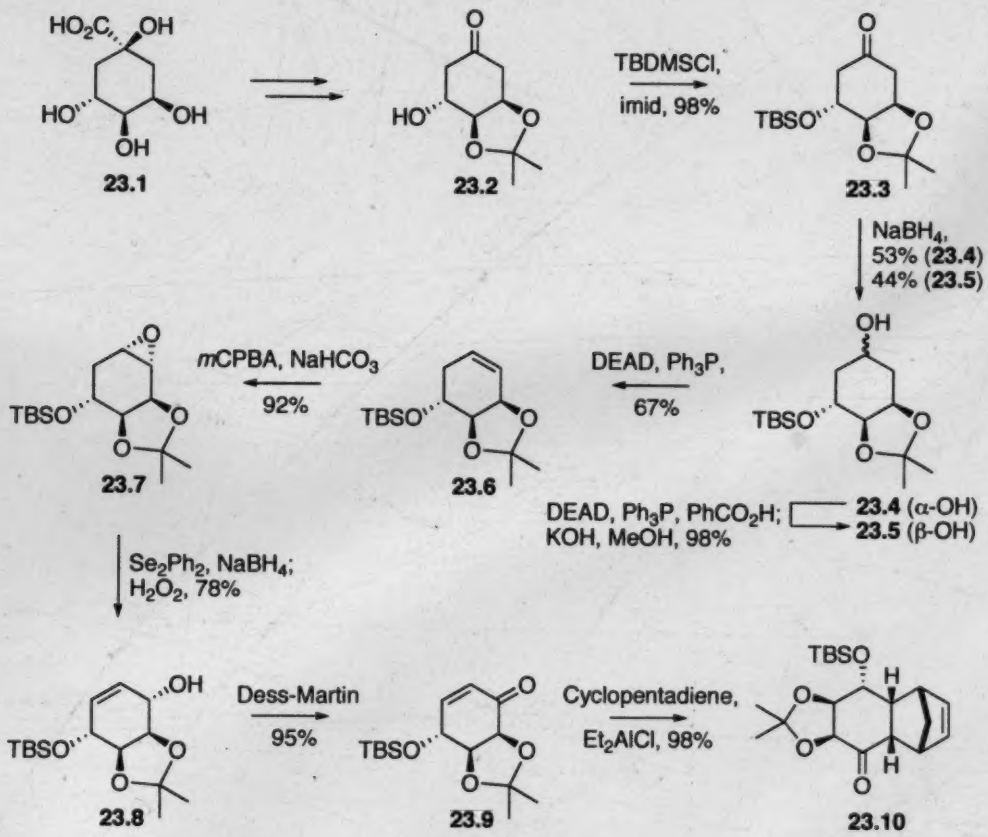
It was found that (+)-**21.9** led to (+)-ottelione A (**5.1**), which had a specific rotation of +19.2 (0.52, $CHCl_3$), the CD spectrum of synthetic ottelione A was also identical with that of the natural product. Treatment of synthetic (+)-ottelione A (**5.1**) with DBU furnished (-)-ottelione B with a specific rotation of -250 (*c* 0.24, $CHCl_3$). *Ent*-ottelione A had a specific rotation of -17 (*c* 0.4, $CHCl_3$) while *ent*-ottelione B had a specific rotation of +246 (*c* 0.4, $CHCl_3$).



Scheme 22

1.3.7 Enantioselective Synthesis of (+)-Ottelione A, (-)-Ottelione B and (+)-3-Epi-Ottelione A by Araki et al.

The total synthesis of ottelione A and B by Araki *et al.* confirms Mehta and Islam's conclusions about the absolute configurations.[21] Like the above syntheses, the Araki approach relies on the cleavage of a bicyclic carbon-carbon bond in an intermediate containing the hydrindane core structure. An epimerization is used to correct the stereogenic center at C-1, but the stereochemistry of centers C-3, C-3a, and C-7a are preserved from the starting bicycle (see below, Scheme 25). The approach is straightforward, but many more steps are needed for blocking and deblocking functionality than in Mehta and Islam's approach. It appears that having a saturated cyclohexane ring in the starting bicyclic system before carbon-carbon bond cleavage (*cf.* **18.3** Scheme 18, with **23.10** Schemes 23 and 24, **12.2** Scheme 12, and **14.2** Scheme 14) paid dividends for Mehta in his total synthesis. Araki *et al.*, unlike Metha and Islam, also experienced difficulty epimerizing the requisite stereocenter from the original bicyclic moiety.

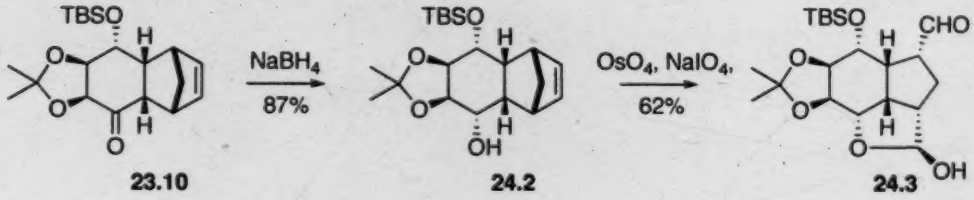


Scheme 23

The synthesis starts with the known enantiomerically pure **23.10** (Scheme 24), which was prepared as shown in Scheme 23.[28] Commercially available (-)-quinic acid (**23.1**), was converted into **23.2**, according to literature procedures.[29] Standard transformations provided **23.5**, which was dehydrated to olefin **23.6**. Epoxidation (**23.6** → **23.7**), followed by conversion to the allylic alcohol **23.8**, oxidation to **23.9**, and formation of the bridged system (containing the five-membered ring of the otteliones, as well as the masked sidearms) was accomplished by Diels-Alder reaction with cyclopentadiene (**23.9** → **23.10**). It is interesting to note that none of the stereogenic centers present in quinic acid

are preserved in the final product, but the stereochemical information is transferred to the hydrindane core during the Diels-Alder reaction.

Thus, reduction of **23.10** (Scheme 24), followed by a Lemieux-Johnson oxidative cleavage (**23.10** → **24.2** → **24.3**), produced cyclic hemiacetal **24.3** by trapping of an intermediate dialdehyde. The free aldehyde moiety reacted chemoselectively with the organolithium generated from **25.2**, to provide a separable mixture of alcohols (**25.3** and **25.4**, Scheme 25).



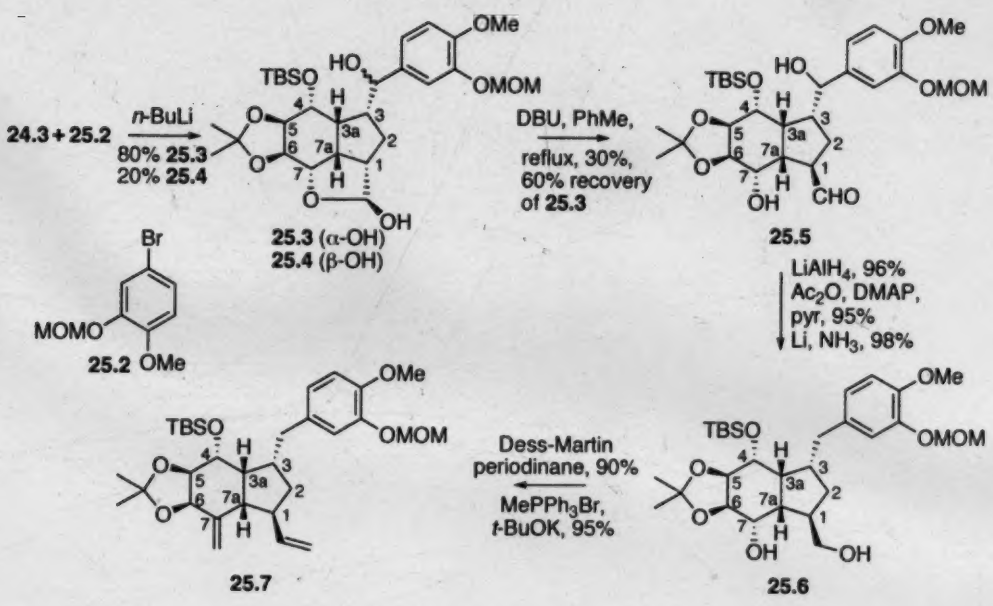
23.10 **24.2** **24.3**

Scheme 24

The base-induced hemiacetal opening/epimerization of the formyl group of **25.3** to provide **25.5** was accomplished using DBU in refluxing toluene for 1.5 h. The yield was 30% under optimized conditions (extended reaction times caused decomposition), and 60% unreacted **25.3** was recovered. This starting material (**25.3**), could be recycled four times to provide *ca* 65% yield of **25.5**. Treatment of the minor lactol **25.4** under identical conditions led to recovery of the starting material, and so the synthesis was carried on using only **25.3**. Since aldehyde **18.4** epimerizes readily, while **14.7** does not, and **25.3** gives a poor yield, it is clear that small structural changes have a profound effect in these bicyclic systems.

Conversion of **25.5** to **25.6** was accomplished in 89% overall yield by formyl group reduction, global acetylation, and reduction with a large excess (100 equiv.) of lithium in liquid ammonia at -78 °C. Double oxidation, followed by double Wittig methylenation provided **25.7**.

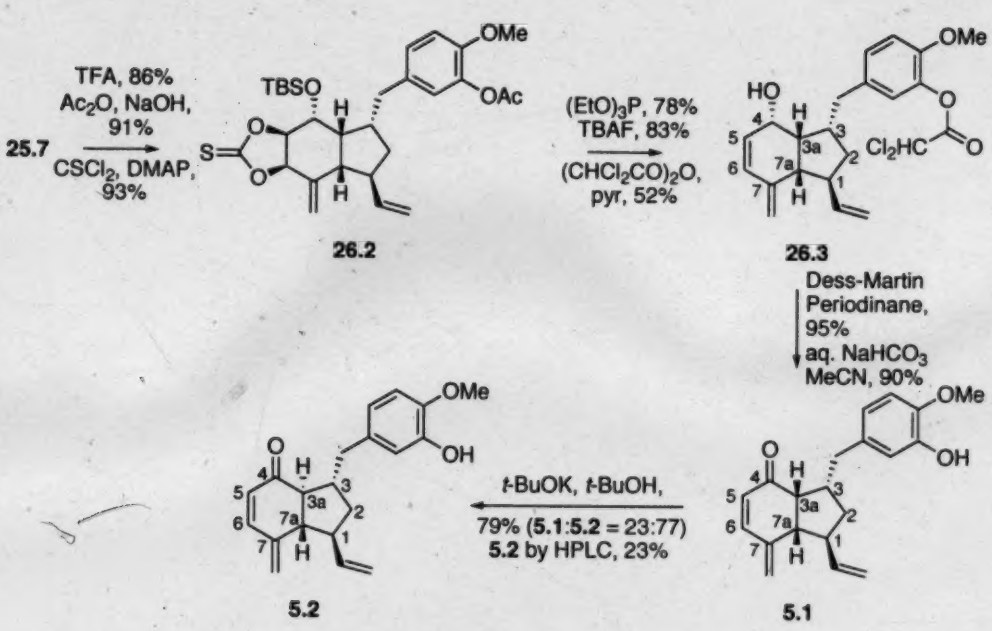
Completion of the synthesis revolves around a multistep sequence to convert the



Scheme 25

three protected aliphatic hydroxyls in **25.7** into the crucial *cis*-dienone system of ottelione A (Scheme 26). Acetonide deprotection was accompanied by removal of the MOM group on the phenolic hydroxyl; the latter was reprotected by chemoselective acetylation. Next, treatment with thiophosgene gave cyclic thiocarbonate **26.2**. Reductive elimination of the thiocarbonate provided the diene system, and this step was followed by fluoride-mediated global deprotection, and reprotection of the phenolic hydroxyl as a dichloroacetate to give **26.3**. The choice of this protecting group was based on the fact that it could be cleanly removed later without epimerization at the C-3a position. Alcohol **26.3** was converted into ottelione A by oxidation and careful deprotection. It was found that the specific rotation was +17.3 (*c* 0.55, $CHCl_3$), comparable to the value found by Mehta and Islam.

However, attempts to convert ottelione A (**5.1**) into ottelione B (**5.2**), using Mehta and Islam's conditions, gave an approximately equal mixture of **5.1** and **5.2**, rather than the claimed complete conversion. The Araki group found that epimerization was best accomplished by exposure to *t*-BuOK in *t*-BuOH at room temperature for 2 h; these

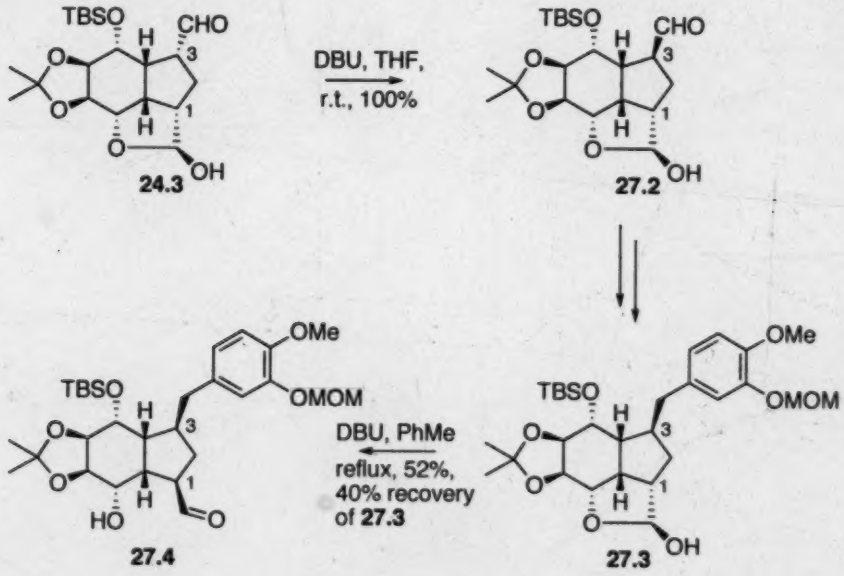


Scheme 26

conditions provided a 23:77 mixture of **5.1** and **5.2**. The isolation of **5.2** was accomplished by high performance liquid chromatography, with a chiral, nonracemic stationary phase. Ottelione B was spectroscopically identical to the other reported data, but the optical rotation was -333.0 (*c* 0.18, $CHCl_3$), significantly higher than that reported by Hoye *et al.*[30] In Hoye's work, **5.2** was contaminated by **5.1** (**5.2**:**5.1** = 85:15) and the material had a specific rotation of -276 (*c* 2.0, $CHCl_3$). It is likely that Mehta and Islam's value for ottelione B [-250 (*c* 0.24, $CHCl_3$)], which is low compared to that of Araki *et al.*, is due to unreported contamination by ottelione A.

Iraki *et al.* also report the synthesis of (+)-**7.1** (3-*epi*-ottelione A), the once favored stereostructure of ottelione A. They use intermediate **24.3** (Scheme 27) and a double side-arm epimerization approach. Epimerization at the C-3 position occurred smoothly to give the thermodynamically favored *exo* isomer (**24.3** → **27.2**) in the presence of DBU at ambient temperature (note the ease of epimerization) in quantitative yield. The coupling

reaction of **27.2** with the aryllithium generated from **25.2** gave a 9:1 mixture of epimeric alcohols (100%). The hydroxyls were removed by deacylation followed by reduction with a large excess (50 equiv.) of lithium in liquid ammonia/THF at -78 °C, providing lactol **27.3** in 87% yield for the two steps. Unlike the above work on ottelione A and B, the critical base-induced lactol-opening/epimerization at the C-1 position in **27.3** went with relative ease. Treatment with DBU in refluxing toluene for 1.5 h, provided **27.4** in 52% yield, along with 40% recovered starting **27.3**. Compound **27.4** was converted into (+)-3-*epi*-ottelione A (**7.1**), using a similar sequence to the above work on ottelione A. The structure was confirmed by extensive 500 MHz ^{1}H NMR spectroscopic analysis, including NOESY experiments.



Scheme 27

In this work protection of the phenolic hydroxyl was done with an acetate (instead of a dichloroacetate, *cf.* **26.2** → **26.3** → **5.1**, Scheme 26) and no complications due to unwanted epimerization at the C-3a position were reported.

Attempted conversion of the 3-*epi*-ottelione A (**7.1**) to 3-*epi*-ottelione B was not discussed in the literature. Similarly, Mehta and Islam have never reported attempted epimerization of an *epi*-ottelione A derivative to the corresponding *epi*-ottelione B derivative. It is possible that in the ottelione system the substitution pattern and relative stereochemistry of the sidearms on the five-membered ring favors epimerization to the *trans* ring fusion in ottelione B, but not in the *epi* series.

2 RESULTS AND DISCUSSION

2.1 Potential Synthetic Approaches to the Trans-Dienone Core

Our interest in ottelione B stemmed from the biological activity and structural novelty of the otteliones. We also believed that ottelione B was a more challenging target than ottelione A.

As mentioned in Section 1.2.3, the *cis*-fused dienone core was known (**9.1**, **9.2**) before the discovery of the otteliones, and the conditions used to generate these structures indicated that they are quite rugged.

Within the ottelione class itself the *cis*-fused dienone was generated by a variety of methods, including the DBU mediated elimination of a mesylate to form the exocyclic double bond (Scheme 11, **11.8** → **11.9**), the phenylselenation-selenoxide elimination sequence (*e.g.* **16.3** → **16.4**, Scheme 16), and oxidation of a diene-alcohol (Scheme 26, **26.3** → **5.1**). These studies also found that the *cis*-core was stable to conditions used to remove phenolic protecting groups. Ironically – from our point of view – the only instability of these systems involved unwanted partial epimerization to the *trans*-fused moiety (**26.2** → **26.3** → **5.1**, Scheme 28). Besides ottelione B, *trans*-fused dienones were unknown, and we suspected that they may suffer easy epimerization to *cis*-isomers, or undergo aromatization. These possibilities provide a possible explanation for the isolation of RPR115781 (**6.2**), rather than ottelione B (**5.2**), by the French group.

It was known that the stability of hydrindanones is influenced by the substitution pattern[22] (as later amply illustrated by synthetic work illustrated above in Schemes 14, 15, and 17) and can be changed by introduction of a double bond.[23] The problem of evaluating the relative stability of *cis* and *trans* fused dienones, as found in the otteliones, however, was not predictable by analogy to known compounds.

Before embarking on a synthesis of ottelione B, we thought it advisable to make the fundamental carbon skeleton **28.1** so as to establish its properties – in particular the stability of the stereogenic center α to the carbonyl and the tendency, if any, of the dienone to aromatize. We would then be able to evaluate conditions that may be used in making the natural product itself.

Synthesis of the model *trans*-dienone moiety would establish the true stability of this system, as there would be no influence on the core by the presence of the ottelione sidearms. It should be noted in retrospect that while Mehta and Islam report the clean epimerization of ottelione A to ottelione B by treatment with base, equivalent transformations involving *epi*-ottelione derivatives (with different relative stereochemistry in the sidearms) have not been reported.

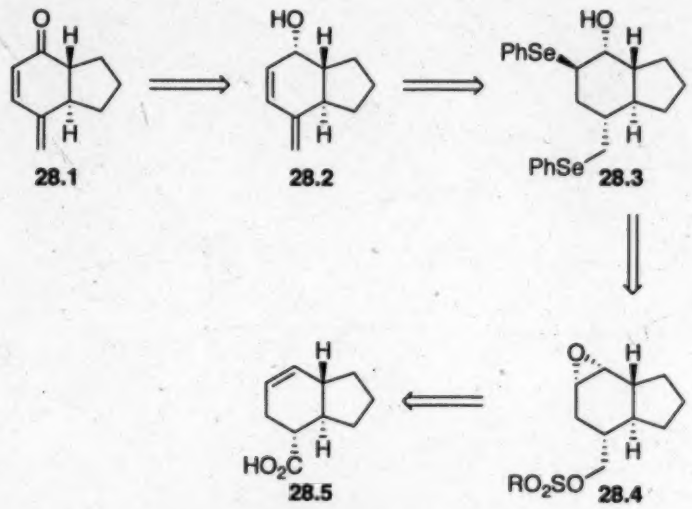
In light of the above considerations, our plan was to synthesize **28.1** through oxidation of **28.2**. We anticipated that the core would be quite robust until this point (Scheme 28). A double selenoxide elimination was planned for generating the diene moiety in **28.2**, and the required bis-selenide **28.3** would be made stereoselectively by simultaneous epoxide-opening and sulfonate displacement. Our starting point was the known acid **28.5**, which contains the hydrindanone core and adequate functionality for further elaboration.

2.2 Synthesis of the Trans-Dienone Core

2.2.1 Preparation of the Advanced Intermediate

The route we selected to make acid **28.5** begins with aldehyde **29.4**, which has been reported several times in the literature. Although we explored several approaches to **29.4**,

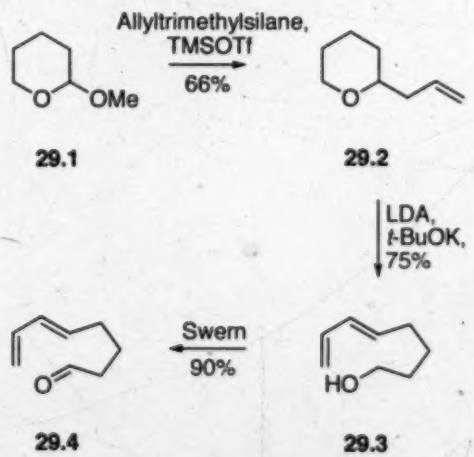
the straightforward sequence shown in Scheme 29, originally described in 1999, served us very well.[31]



Scheme 28

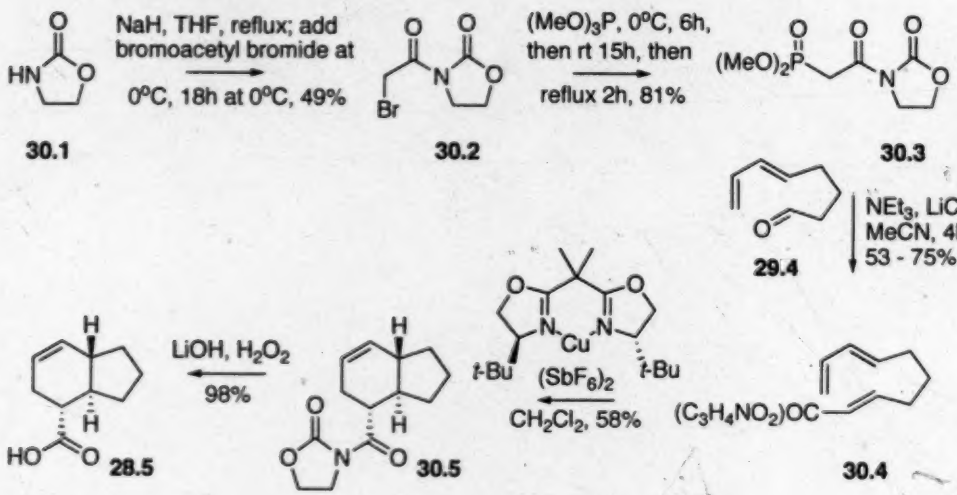
The known phosphonate **30.3** was then made as indicated in Scheme 30.[32]

Olefination of (5*E*)-5,7-octadienal (**29.4**) with **30.3** gave the expected triene. However, we



Scheme 29

initially experienced some difficulty in preparing **30.3**. The reported procedure for the conversion of **30.1** to **30.2**, had to be modified,[33] and very vigorous mechanical stirring was required to obtain a yield above *ca* 25%. Evans *et al*. describe doing the Arbuzov reaction (**30.2** → **30.3**) at reflux,[32] but in our hands this protocol caused the reaction mixture to erupt violently from the flask; and we found this reaction should be done initially with ice bath cooling (for 6 h), and then at room temperature with a water bath (for an arbitrary period of 15 h), before the reflux period (2 h).



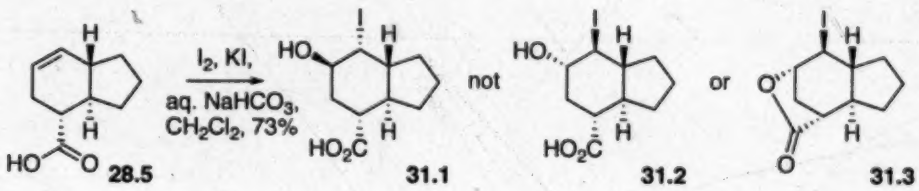
Scheme 30

The intramolecular Diels-Alder reaction, using the modern procedure of Evans,[32] assembled the *trans* ring fused core. Exposure of triene **30.4** to the action of the chiral catalyst [Cu(*S*,*S*)-*t*-Bu-box](SbF$_6$)$_2$, which was prepared in three steps from *t*-butyl leucine, provided **30.5** in variable yields, presumably depending on the quality of the catalyst. The reaction was slower than that reported in the literature (even with higher catalyst loading), and reaction times of one week were typically necessary. The yields varied from 43% yield of **30.5** plus 47% recovered **30.4**, to 58% of **30.5** with no **30.4** recovered, but a large amount of a polymer formed. Material prepared in this way is reported to have an ee of 86%,[32] but

we did not measure the optical purity of our compounds in this study. Detachment of the auxiliary (98%) liberated our starting acid **28.5**.[34]

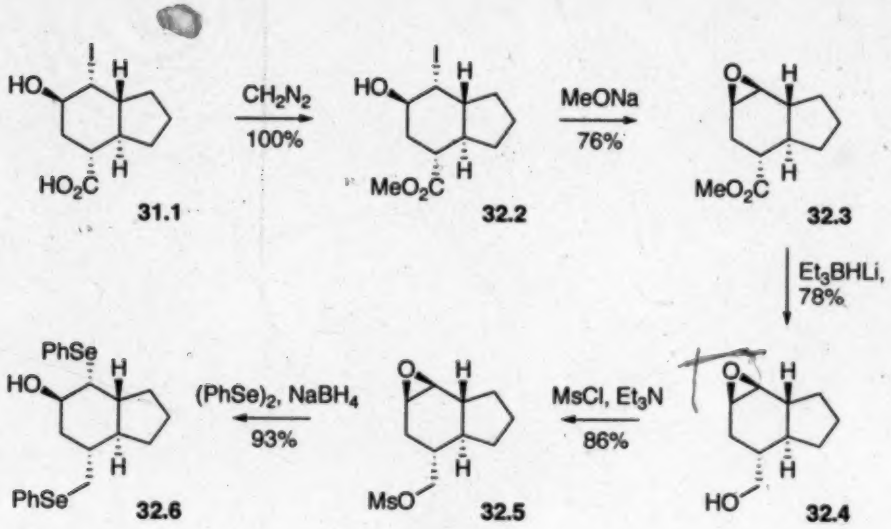
2.2.2 Attempted Elaboration to the Dienone Core

Initial attempts to elaborate **28.5** into **28.1** were problematic. Our first approach was to attempt the iodo-lactonization of **28.5** so as to form compound **31.3**. Instead, we obtained iodo alcohol **31.1** (Scheme 31). The stereo- and regiochemistry of **31.1** were not immediately obvious, but the structure was latter established to be as shown. Initially, we thought we had made **31.2**, and we assumed that it arose from the expected product **31.3** by hydrolysis under the reaction conditions.



Scheme 31

On the basis of our erroneous structural assignment we esterified the acid (now known to be **31.1**) with diazomethane to obtain **32.2** (100%). Treatment with base then generated epoxide **32.3**. As a consequence of the stereochemistry of **32.3**, *trans*-diaxial opening of the epoxide ring would give a selenide with the opposite regiochemistry needed to form the required dienone system. Still ignorant of the fact that our epoxide had structure **32.3**, we selectively reduced the ester moiety, using LAH (47%) or in better yield by using a deficiency of Super-Hydride (78%). Mesylation under standard conditions then gave **32.5** (86%), and treatment of this material with an excess of PhSeNa provided bis-selenide **32.6** in excellent yield.



Scheme 32

Attempts at selenoxide oxidation did not provide the expected dienone **28.2** (see Scheme 28), and this observation suggested that we had misassigned one or more of the structures. Fortunately, we were able to obtain a single crystal X-ray analysis (Figure 1) of

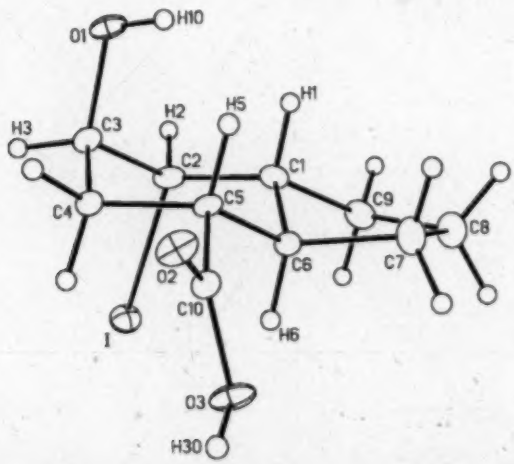


Figure 1: Single crystal X-ray analysis of (3a*S*,4*R*,6*R*,7*R*,7a*R*)-Octahydro-6-hydroxy-7-iodo-1*H*-indene-4-carboxylic Acid (31.1)

31.1, which revealed the actual stereochemistry of the compound.

The extensive precedent for the course of iodolactonization (which would be expected to give **31.3** or **31.2**) caused us to go back and confirm the structure of acid **28.5**, also by X-ray crystallography (Figure 2).

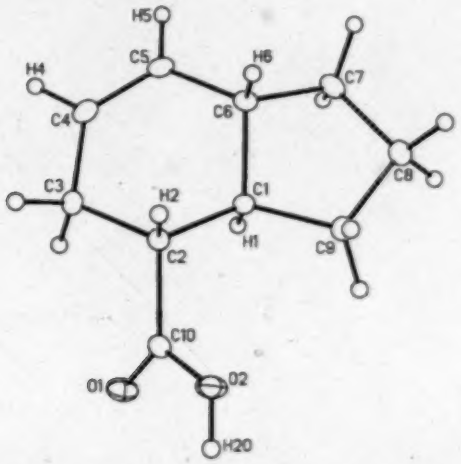
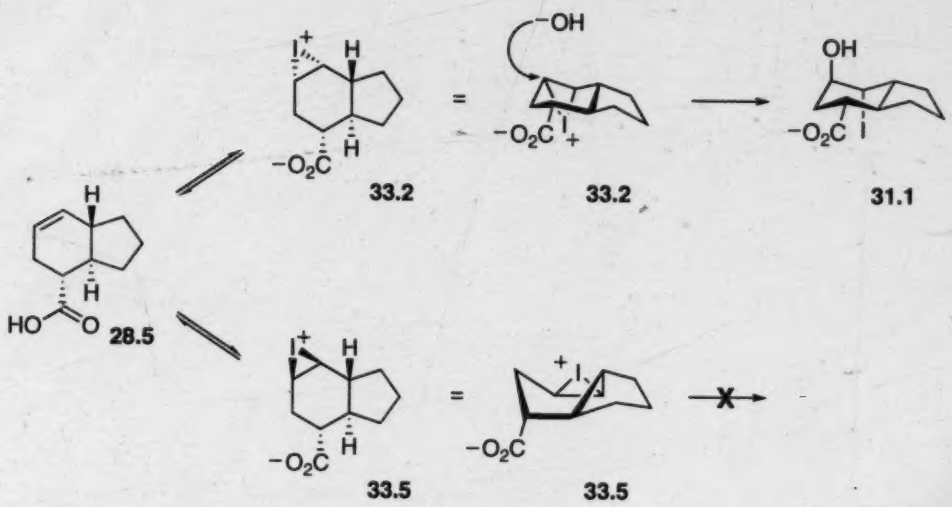


Figure 2: Single crystal X-ray analysis of (3a*R*,4*R*,7a*S*)-2,3,3a,4,5,7a-Hexahydro-1*H*-indene-4-carboxylic Acid (28.5)

The formation of iodohydrins from olefins is known,[35] but the normal outcome in the presence of a suitably placed carboxyl is iodolactonization. In the present case, however, inspection of Dreiding models shows that generation of an iodonium ion (**33.5**) on the β-face of **28.5**, and intramolecular trapping must proceed by way of a boat-like six-membered ring (Scheme 33), and either of the resulting lactones would be highly strained. In contrast, these unfavorable geometrical changes are avoided by formation of an α-iodonium ion (**33.2**), followed by intermolecular *trans* diaxial ring opening by water or HO^-, leading to **31.1**. The positive charge on an iodonium ion such as **33.2** may well be stabilized by the negatively charged carboxylate.[36]

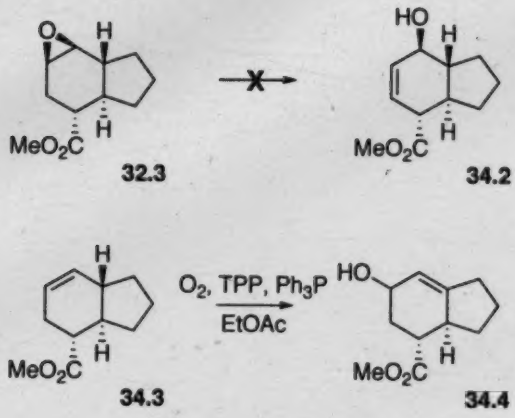


Scheme 33

Other attempts to directly generate an α-epoxide, as required by our synthetic plan, were unfruitful. MCPBA oxidation of methyl ester **34.3**, gave a 2.5:1 ratio of epoxides, in favor of the undesired β-epoxide. The Sharpless $VO(acac)_2$-directed epoxidation with *t*-BuOOH, applied to the alcohol derived from **28.5**, provided a complex mixture of products. We were later (Scheme 37) able to generate an epoxide of the desired stereochemistry through an indirect method. We were unsuccessful in direct conversion of epoxide **32.3** to the appropriate allylic alcohol **34.2** (Scheme 34) under a variety of acidic or basic conditions. Singlet oxygen oxidation of **34.3** led to the undesired regioisomer **34.4** as the major product, which was obtained in very low conversion, even after extended reaction times.

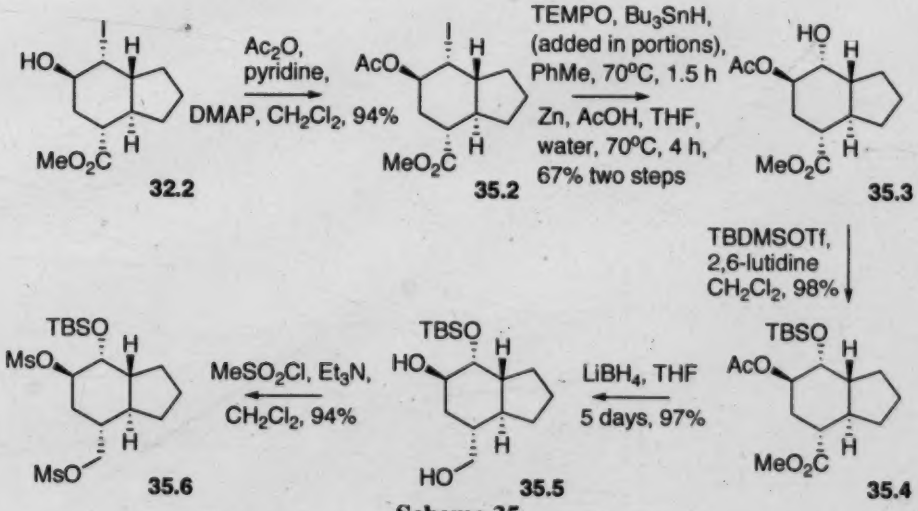
2.2.3 Two Related Routes to the Dienone Core

Eventually, we were able to reach our target molecule by an indirect route involving replacement of the iodine moiety by a hydroxyl group. This route begins with acetylation of **32.2** to gave iodide **35.2** (Scheme 35). The halogen was stereoselectively replaced by a



Scheme 34

hydroxyl (**35.2** → **35.3**), using a standard two-step free radical method (67%) where Bu_3SnH and AIBN were added in portions alternating with portions of TEMPO.[37] The labile N-O bond of the TEMPO adduct was then cleaved, using the conditions shown. Silylation (**35.3** → **35.4**) of the hydroxyl moiety and double reduction of the acetate units ($LiBH_4$, 97%) provided crystalline diol **35.5**.



Scheme 35

The diol was subjected to X-ray analysis to confirm the structure (Figure 3), as we experienced difficulty eliminating these alcohols to the corresponding olefins, using standard procedures. From this point we developed two related routes towards the dienone; both involve conversion of diol **35.5** to bis-mesylate **35.6**.

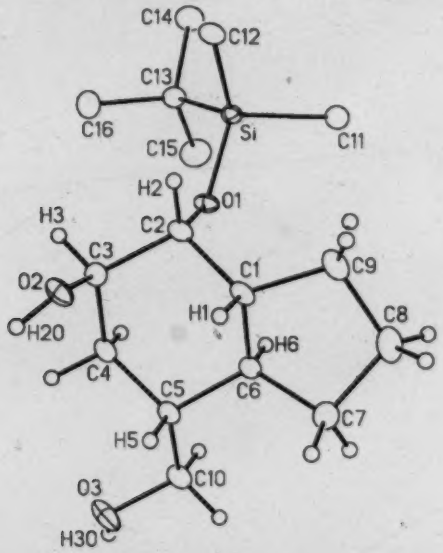
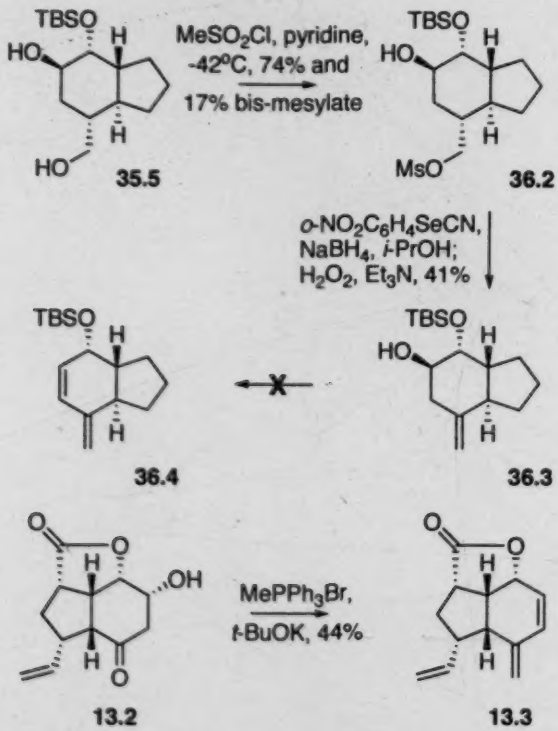


Figure 3: Single crystal X-ray analysis of (3a*S*,4*R*,6*R*,7*R*,7a*R*)-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-octahydro-6-hydroxy-1*H*-indene-4-methanol (35.5)

Exploratory experiments that reliably allowed us to convert one of the alcohols into an olefin are shown in Scheme 36. The yields are modest, but elimination of the other alcohol would have produced a double bond in conjugation with the exocyclic olefin — exactly as desired.

Although we were later (see Scheme 38) able to eliminate the mesylate derived from **36.3** under forcing conditions (DBU in refluxing *o*-xylene), use of DBU in refluxing PhMe provided only unreacted starting material, even after 3 days. Other attempts to effect direct elimination of alcohol **36.3**, including basic, acidic and free radical methods were

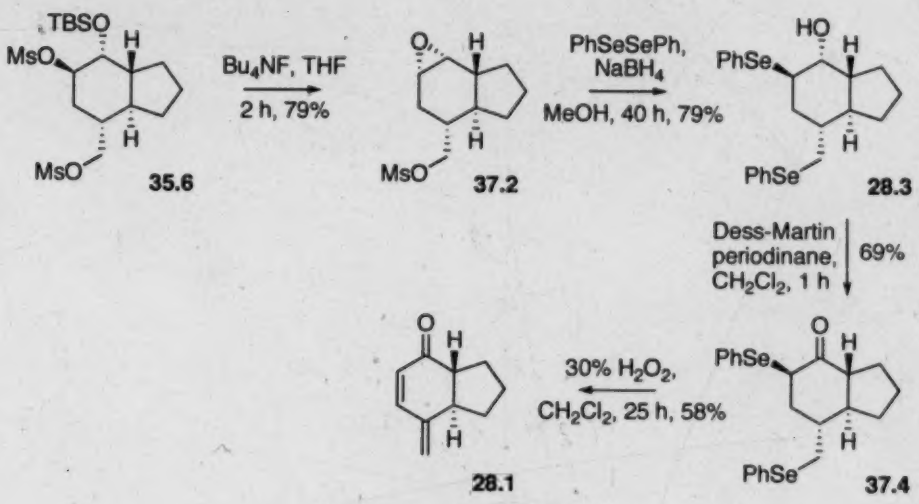
unsuccessful. Treatment with Martin's sulfurane and with the Burgess reagent, led in both cases to the isolation of products where part of the reagent had become covalently attached to the alcohol moiety. We found that even in the case of the triflate derived from **36.3**, we could not accomplish an intermolecular displacement with $PhSe^-$.[38] These results are in contrast to the ease of elimination observed during Mehta's Wittig reaction with **13.2** (**13.2** → **13.3**, Scheme 36). Presumably, there are conformational factors that cause the transformation **36.3** → **36.4** to be very difficult.



Scheme 36

Eventually, use of bis-mesylate **35.6**, a key intermediate in our synthesis, led to successful approaches to the target. Desilylation readily provides the elusive α-epoxide **37.2** and, on treatment with PhSeNa, the bis-selenide **28.3** was obtained (81%). In order to

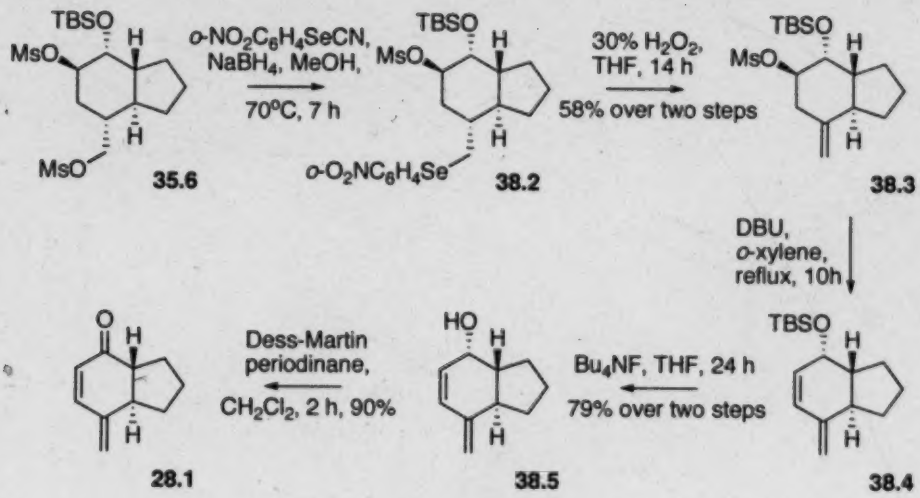
facilitate the subsequent selenoxide elimination, the hydroxy group was chemoselectively oxidized (**28.3** → **37.4**, Dess-Martin reagent, 69%), and then treatment with hydrogen peroxide afforded the target ketone **28.1** (58%).



Scheme 37

Bis-mesylate **35.6** was also converted into **38.2** by the reactions summarized in Scheme 38. The primary methanesulfonyloxy group was displaced (**35.6** → **38.2**) with *o*-$O_2NC_6H_4Se^-$ (5 equiv.), and selenoxide elimination then produced the exocyclic olefin **38.3** [58% from **35.6**, after correction for recovered **35.6** (11%)]. Treatment with DBU in refluxing *o*-xylene now served to generate the diene system **38.4**, which was not isolated because the low polarity and low boiling point of **38.4** made its separation from *o*-xylene impractical. Finally, desilylation to release alcohol **38.5** (79% from **38.3**), followed by oxidation, again with the Dess-Martin reagent, afforded **28.1** (90%).

The dienone (**28.1**) is a low melting (34 °C) crystalline solid, which was recovered unchanged after aqueous work up, and silica gel chromatography. Distillation at about 170 °C could also be used to purify this compound.



Scheme 38

2.2.4 Proof of Stereochemistry of the Trans-Dienone Core

At this point we had to prove that we had indeed made the *trans* ring fused material and that no epimerization had occurred in the steps **28.3** → **37.4** → **28.1** (Scheme 37), or **38.5** → **28.1** (Scheme 38). Ketone **28.1** was also obtained when we used a very gentle method for the oxidation of **38.5**. Treatment with MnO_2 in CD_2Cl_2 followed by filtration and immediate ^1H NMR analysis provided the same product obtained in the other transformations.

Although **28.1** was crystalline, we were unable to obtain material suitable for X-ray analysis. The crystals of the alcohol derived from Luche reduction (**39.2**, Scheme 39) and the *p*-nitrobenzoate derived from **39.2**, were also unsatisfactory for analysis.

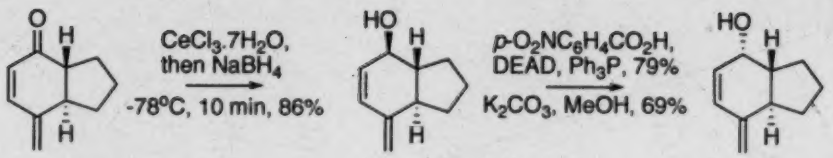
Extensive 2D NMR (500 MHz) data tentatively indicated that the coupling constants between the two ring junction protons is about 14.1 Hz, a value which does suggest *trans* ring fusion, but more definitive proof of the structure of **28.1** was sought.

We reasoned that if we could generate the corresponding *cis* isomer then we could compare and contrast the spectroscopic data of the two isomers.

Attempts to isomerize **28.1** to the *cis* isomer by treatment with 3 equivalents of $TsOH.H_2O$ in THF at room temperature for 12 h produced no change. By increasing the reaction temperature to reflux for 1 h we obtained 15% of an unknown decomposition product, about 75% of the starting material and about 10% of what may be the *cis* isomer (^{1}H NMR). Deprotonation with LDA followed by reprotonation by AcOH provided an 83:17 mixture favoring the starting material. In both cases we were unable to separate **28.1** from what we believe was the *cis* isomer. Although other conditions were used to attempt generation of the *cis* isomer those given above were the only ones that did not lead to complex mixtures.

As we had instinctively expected the *cis* isomer to be more stable than the *trans*, and were concerned that epimerization may immediately occur upon formation of **28.1**, we asked Professor Klobukowski of this Department to perform calculations to help guide interpretation of the above results. *Ab initio* Density Functional Theory calculations using the 6-31G* basis set indicated that in the gas phase the *cis* and *trans* isomers of **28.1**, have equal energies (±1 kcal/mol, the energies were not modified for zero-point energy corrections). This was a surprising result.[39]

We began to work on a synthesis of the *cis* dienone, but this was ultimately unnecessary as we were able to degrade **28.1** to a known compound of established stereochemistry. Reduction of **28.1** occurred extremely rapidly (< 10 min at -78 °C) with $NaBH_4/CeCl_3.7H_2O$, and provided a 23:1 (^{1}H NMR) mixture of alcohols in favor of **39.2** (Scheme 39). The minor alcohol was spectroscopically identical to alcohol **38.5**. Mitsunobu inversion[40] converted the major alcohol **39.2** into **38.5**, whose structure and stereochemistry can be assigned with certainty on the basis of X-ray data obtained on its precursor **35.5** (Scheme 35), and the steps used to generate **38.5** from **35.5**. These observations show that no change in ring fusion stereochemistry occurs in any of the steps involving generation or manipulation of ketones **37.4** or **28.1**.



28.1 **39.2** **38.5**

Scheme 39

3 CONCLUSION

We were able to devise two related syntheses of the unsubstituted core of ottelione B. Our results show that the substituents of ottelione B are not essential to stabilize the dienone substructure. The *trans* ring fused dienone **28.1**, appears to be quite robust, and we never detected the presence of the more thermodynamically stable aromatic tautomer.

4 FUTURE RESEARCH

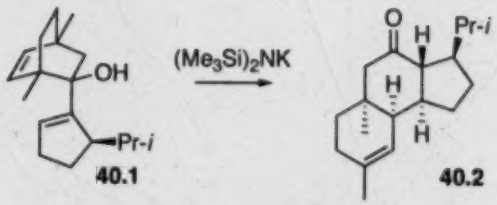
While our work was in press,[41] it was reported that ottelione A, originally thought to have structure **7.1** or **7.2**, actually had structure **5.1**, and that this material is readily convertible to ottelione B (**5.2**). This report caused us to abandon our plan to synthesize ottelione B, as Mehta's synthetic route is efficient, and elegant, and provides both otteliones. However, it now appears that this conversion is not at all easily achieved, and the mixture of otteliones produced must be separated by HPLC.

In our work, epimerization of **28.1** to the *cis* fused material is not readily achieved. It is possible that the particular stereochemical and substituent arrangement present in the otteliones may facilitate epimerization to a mixture of ottelione A and ottelione B. Epimerization of a *cis* to a *trans* ring fused dienone system has only been reported in the specific case of **5.1** → **5.2**, despite the accumulating published work on ottelione A and its epimers.

Access to ottelione A, analogs of ottelione A, and to ottelione B itself is available by the published routes of the Mehta and Araki groups. However, using these routes, the

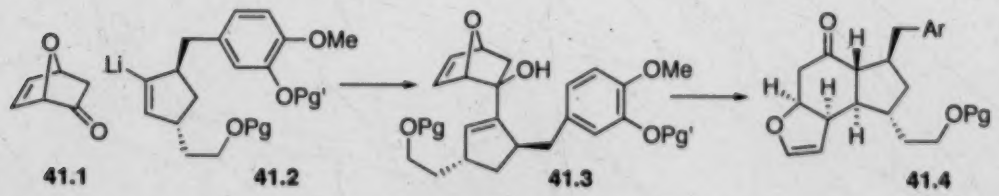
analogues of ottelione B that are available for future structure-activity relationship studies may be limited to structures having the same relative stereochemistry on the five-membered ring. A total synthesis of ottelione B - better suited for adaptation toward analogues - could provide access to many important derivatives for biological screening. This would be a worthwhile endeavor even though ottelione A is a more powerful antitumor agent.

The relative stability of *cis* and *trans* ring fused hydrindanones depends on the substitution pattern. Based on Mehta's report that epimerization of **17.2** to **17.4** (Scheme 17), and **14.7** → **14.8** (Scheme 14) are spontaneous, the same stereochemical outcome of the oxy-Cope rearrangement reported by Paquette for **40.1** → **40.2**,[42] would likely be followed in a system related to the otteliones.



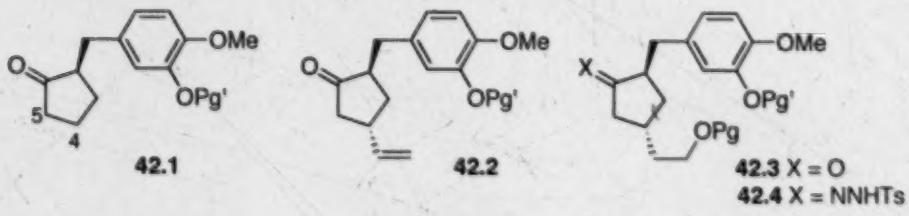
Scheme 40

This possibility provides the basis for a new synthesis of ottelione B along the following lines. Reaction conditions have been developed by others[43] to allow the joining of ketone **41.1** with molecules related to **41.2**, to give **41.3**. Subjection of **41.3** to anionic oxy-Cope reaction conditions, should generate tricyclic ketone **41.4**, whose stereochemistry



Scheme 41

is anticipated to be as shown, by analogy with **40.2**. Cleavage of the double bond in the oxygen-containing ring of **41.4** should release functionality (OH and CHO) that will allow generation of the conjugated double bonds of ottelione B. Our work on the skeleton provides a model to help define acceptable reaction conditions. Further, protection of the carbonyl moiety in compounds derived from **41.4** may not be necessary, as epimerization to the *cis* fused material may be unfavored. However, temporary reduction of the ketone carbonyl would provide adequate robustness to the core unit, if necessary. The best choice of protecting groups Pg and Pg' will probably be hindered silicon groups or MOM units. A key problem will be the synthesis of optically pure **41.2**, and this would likely be approached by asymmetric alkylation of cyclopentanone to form **42.1**, followed by desaturation at C-4-C-5, conjugate addition using lithium divinylcuprate (to give **42.2**), and then hydroboration and protection. The resulting ketone (**42.3**) will be converted into its tosyl hydrazone **42.4**, from which the lithium salt **41.2** will be generated using BuLi.



Scheme 42

This route should provide ottelione B and enough flexibility so as to allow the synthesis of analogues for biological study.

5 EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage

through a column (3.5 x 42 cm) of R-311 catalyst and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (140 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar or N_2. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane and ethyl acetate used for chromatography were distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Air was then drawn through for 1 min and the syringe was stored under vacuum. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar or N_2), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid, followed by charring with a heat gun, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF, Et_2O, PhH, PhMe and dioxane were distilled from sodium and benzophenone ketyl. Dry CH_2Cl_2, Et_3N, *i*-Pr_2NEt and pyridine were distilled from CaH_2. Dry MeOH was distilled from $Mg(OEt)_2$. Acetone was distilled from K_2CO_3.

FT-IR measurements were made from the specified solvent using KBr plates.

The symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, as based on the APT experiment.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

(3a*R*,4*R*,7a*S*)-2,3,3a,4,5,7a-Hexahydro-1*H*-indene-4-carboxylic Acid (28.5).

30.5 **28.5**

LiOH·H_2O (14.0 mg, 0.334 mmol) was added in one portion into a stirred and cooled (0 °C) solution of H_2O_2 (30% w/v, 0.025 mL, 0.29 mmol) and **30.5** (27.0 mg, 0.114 mmol) in 3:1 THF-water (2.35 mL). The cooling bath was removed after 40 min, and stirring was continued for 4 h. Aqueous $Na_2S_2O_3$ (1.0 M, 1 mL) was added and the mixture was extracted with CH_2Cl_2. The aqueous phase was acidified (pH *ca* 1) and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated to produce a slightly yellow solid that is suitable for the next step. Flash chromatography of the residue over silica gel, using 3:10 EtOAc-hexane and a trace (1 drop in 100 mL) of HCO_2H, gave **28.5** (18.7 mg, 98%) as a white solid.[44] X-ray analysis was carried out on a sample crystallized from Et_2O: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12-1.31 (m, 2 H), 1.55 (dq, J = 6.3, 11.3 Hz, 1 H), 1.66-1.74 (m, 2 H), 1.82-1.94 (m, 2 H), 2.31-2.45 (m, 2 H), 2.53 (dt, J = 6.3, 10.9 Hz, 1 H), 5.57 (dq, J = 9.9, 2.8 Hz, 1 H), 5.82 (dq, J = 9.8, 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.9 (t), 28.2 (t), 29.0 (t), 29.8 (t), 44.2 (d), 44.3 (d), 49.6 (d), 125.2 (d), 129.7 (d), 182.1 (s).

(3a*S*,4*R*,6*R*,7*R*,7a*R*)-Octahydro-6-hydroxy-7-iodo-1*H*-indene-4-carboxylic Acid (31.1).

28.5 **31.1**

I_2 (0.80 g, 3.1 mmol) and KI (0.26 g, 1.6 mmol) were ground together into a fine powder and transferred into a round-bottomed flask, protected from light by aluminum foil. The powder was covered with CH_2Cl_2 (10 mL) and water (10 mL), and the mixture was stirred for 10 min. Both phases were then added into a stirred mixture of **28.5** (0.230 g, 1.217 mmol) and $NaHCO_3$ (0.281 g, 3.34 mmol) in water (10 mL) and CH_2Cl_2 (10 mL). The reaction flask was protected from light, and stirring was continued for 13 h. The layers were separated and the aqueous phase was extracted with $CHCl_3$ (20 mL) and then acidified to pH 1 and extracted with more $CHCl_3$ (4 x 20 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ (0.5 M, 20 mL), dried ($MgSO_4$), and evaporated. While this material was used directly in the next step, a pure sample of **31.1** was obtained by flash chromatography over silica gel, using 40 to 80% EtOAc-hexane. The compound was obtained as a white solid. A portion was recrystallized from CH_2Cl_2 and subjected to X-ray analysis: FTIR ($CHCl_3$, cast) 2955, 2870, 1703, 1439, 1284, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.16 (apparent tq, *J* = 11.1, 3.4 Hz, 1 H), 1.27-1.37 (m, 2 H), 1.61-1.72 (m, 4 H), 1.94-2.03 (m, 2 H), 2.45 (td, *J* = 12.8, 2.3 Hz, 1 H), 2.64 (ddd, *J* = 1.5, 11.2, 3.6 Hz, 1 H), 4.45 (q, *J* = 2.8 Hz, 1 H), 4.56 (apparent dd, *J* = 2.8, 1.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2 (t), 28.9 (t), 30.6 (t), 31.8 (t), 42.0 (d), 42.1 (d), 42.5 (d), 43.5 (d), 72.6 (d), 180.1 (s); exact mass *m/z* calcd for $C_{10}H_{15}O_3$ (M - I) 183.10213, found 183.10247.

Methyl (3a*S*,4*R*,6*R*,7*R*,7a*R*)-Octahydro-6-hydroxy-7-iodo-1*H*-indene-4-carboxylate (32.2).

31.1 **32.2**

An excess of ice-cold ethereal CH_2N_2 (*ca* 0.3 M in Et_2O) was pipetted into a flask containing the crude iodo alcohol from the previous reaction, and the mixture was stirred at room temperature for 20 min (TLC control, 1:1 EtOAc-hexane), by which time reaction was complete. The yellow solution was evaporated under reduced pressure (water pump), and flash chromatography of the residue over silica gel, using 20% EtOAc-hexane, gave **32.2** (0.276 g, 73% over two steps) as a clear, colorless oil: FTIR ($CHCl_3$, cast) 3450, 2949, 2869, 1734, 1712, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.23 (apparent tq, J = 11.2, 3.0 Hz, 1 H), 1.22-1.35 (m, 2 H), 1.59-1.72 (m, 4 H), 1.86-1.96 (m, 2 H), 2.0 (br s, 1 H), 2.42 (tq, J = 14.3, 1.4 Hz, 1 H), 2.60 (tm, J = 12.9 Hz, 1 H), 3.63 (s, 3 H), 4.43 (q, J = 2.8 Hz, 1 H), 4.55 (q, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2 (t), 28.9 (t), 30.7 (t), 31.8 (t), 42.3 (d), 42.4 (d), 42.6 (d), 43.76 (d), 43.77 (d), 72.7 (d), 175.3; exact mass *m/z* calcd for $C_{11}H_{17}O_3I$ 324.02225, found 324.02128.

Methyl (3a*S*,4*R*,6*R*,7*R*,7a*R*)-6-(Acetoxy)octahydro-7-iodo-1*H*-indene-4-carboxylate (35.2).

32.2 **35.2**

Pyridine (0.89 mL, 11 mmol) was added in one portion into a stirred solution of **32.2** (0.678 g, 2.19 mmol) and Ac_2O (1.03 mL, 10.9 mmol) in CH_2Cl_2 (30 mL) at room temperature. A few small crystals of DMAP were added and stirring was continued overnight. The reaction was quenched by addition of saturated aqueous NH_4Cl (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL), and the combined extracts were dried ($MgSO_4$), and evaporated. Residual solvent was removed under oil pump vacuum overnight to give **35.2** (0.770 g, 96%) as a pure oil.

This material can be obtained in 77% yield from **31.1** (0.010 mol scale) by carrying out a purification (flash chromatography over silica gel, using 1:10 EtOAc-hexane as eluant) only at this last stage: FTIR ($CDCl_3$, cast) 2953, 1737, 1371, 1268, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.81 (tq, J = 11.2 Hz, 1 H), 1.24-1.36 (m, 2 H), 1.61-1.74 (m, 4 H), 1.88-2.02 (m, 2 H), 2.06 (s, 3 H), 2.43-2.54 (m, 2 H), 3.68 (s, 3 H), 4.59 (dd, J = 4.4, 3.0 Hz, 1 H), 5.35 (q, J = 2.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.16 (q), 21.19 (t), 28.3 (t), 28.9 (t), 31.8 (t), 37.4 (d), 42.2 (d), 43.8 (d), 44.4 (d), 51.7 (q), 74.2 (d), 169.3 (s), 174.6 (s); exact mass m/z calcd for $C_{13}H_{19}NaO_4I$ (M + Na) 389.02203, found 389.02146.

Methyl (3a*R*,4*R*,6*R*,7*R*,7a*R*) 6-(Acetoxy)octahydro-7-hydroxy-1*H*-indene-4-carboxylate (35.3).

35.2 **35.3**

Bu_3SnH (0.18 mL, 6.8 mmol) was added in one portion into a solution of **35.2** (0.249 g, 0.682 mmol) and TEMPO (freshly sublimed, 0.570 g, 3.65 mmol) in PhMe (20 mL). The solution was warmed to 70 °C, and an additional equivalent of Bu_3SnH (0.18 mL) was added after 15 min. After another 15 min, TEMPO (0.323 g, 2.07 mmol) was added quickly in one portion, followed immediately by Bu_3SnH (0.18 mL). After a further 15 min, another portion of Bu_3SnH (0.18 mL) was added, and this addition was repeated once more after an additional 15 min. Stirring was continued for 30 min after the last addition, and the solution then cooled and evaporated. Flash chromatography of the residue over silica gel, using increasing amounts (0-10%) of EtOAc in hexane served to remove most of the tin residues. The resulting material was dissolved in 3:1:1 AcOH-THF-H_2O (35 mL), and Zn dust (0.558 g, 8.54 mmol) was added. The resulting suspension was

warmed to 70 °C with vigorous stirring. The mixture was cooled to 25 °C after 4 h, and the Zn was removed by filtration. The solvent was evaporated and the residue was dissolved in EtOAc and filtered. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 30% EtOAc-hexane, gave **35.3** (0.054 g, 30%) as an oil, and some of the TEMPO adduct from the first step. The TEMPO adduct was resubmitted to the above conditions to give an additional batch (62.6 mg) of **35.3** (total yield = 0.1164 g, 67% over two steps). During chromatography a small amount of the diastereomeric alcohol is eluted after **35.3**; it is easily separated and not used, no yield was measured). Compound **35.3** had: FTIR (CH_2Cl_2, cast) 3506, 2954, 2874, 1735, 1437, 1374 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.15-1.24 (m, 1 H), 1.50-1.67 (m, 4 H), 1.73-1.92 (m, 4 H), 1.97-2.09 (m, 1 H), 2.03 (s, 3 H), 2.37 (td, J = 12.1, 3.7 Hz, 1 H), 3.65 (s, 3 H), 4.92 (br s, 1 H), 4.99 (q, J = 2.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2 (t), 21.3 (q), 24.6 (t), 28.4 (t), 29.4 (t), 39.2 (d), 44.2 (d), 44.3 (d), 51.6 (q), 67.2 (d), 72.3 (d), 169.9 (s), 175.3 (s); exact mass m/z calcd for $C_{13}H_{20}O_5$ 256.13107, found 256.13086.

Methyl (3a*R*,4*R*,6*R*,7*R*,7a*R*)-6-(Acetoxy)-7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]octahydro-1*H*-indene-4-carboxylate (35.4).

35.3 **35.4**

t-$BuMe_2SiOSO_2CF_3$ (0.55 mL, 2.4 mmol) was injected at a fast, dropwise rate into a stirred and cooled (ice-water bath) solution of **35.3** (0.2312 g, 0.9027 mmol) and 2,6-lutidine (0.35 mL, 3.0 mmol) in dry CH_2Cl_2 (10 mL). Stirring was continued for 4 h (ice bath) (TLC control, silica, 1:5 EtOAc-hexane), the ice bath was removed and stirring was continued for 15 h. Water (50 mL) was added and the mixture extracted with CH_2Cl_2 (2 x

20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 1:10 EtOAc-hexane, gave **35.4** (0.3273 g, 98%) as a sticky oil: FTIR ($CHCl_3$, cast) 2955, 2929, 2857, 1733, 1373, 1240, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.03 (s, 3 H), 0.10 (s, 3 H), 0.89 (s, 9 H), 1.13 (m, 1 H), 1.45-1.63 (m, 5 H), 1.74-1.86 (m, 3 H), 1.95-2.02 (m, 1 H), 2.03 (s, 3 H), 2.32-2.38 (m, 1 H), 3.65 (s, 3 H), 3.83 (d, J = 3.4 Hz, 1 H), 4.86 (q, J = 3.1 Hz], 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.2 (q), -4.8 (q), 18.0 (s), 21.1 (t), 21.2 (q), 25.1 (t), 25.8 (q), 28.4 (t), 29.1 (t), 39.3 (d), 44.0 (d), 44.8 (d), 51.4 (q), 67.7 (d), 72.4 (d), 169.9 (s), 175.6 (s); exact mass *m/z* calcd for $C_{15}H_{25}O_5Si$ (M - C_4H_9) 313.14713, found 313.14644.

3a*S*,4*R*,6*R*,7*R*,7a*R*)-7-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-6-hydroxy-1*H*-indene-4-methanol (35.5).

35.4 **35.5**

$LiBH_4$ (2.0 M in THF, 3.4 mL, 6.8 mmol) was added rapidly by syringe into a stirred solution of **35.4** (0.2123 g, 0.5728 mmol) in THF (20 mL). Stirring was continued for 117 h, during which time 3 more portions of $LiBH_4$ (2.0 M in THF, each 1.7 mL, 3.4 mmol) were added 25, 64 and 113 h after the initial addition. The mixture was quenched carefully with water (20 mL) and, after hydrogen evolution had ceased, brine (20 mL) and EtOAc (20 mL) were added. The mixture was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 50% EtOAc-hexane, gave **35.5** (0.1674 g, 97%) as a white solid. A sample was recrystallized from *i*-Pr_2O for X-ray analysis: mp 167-170 °C; FTIR

(CH_2Cl_2, cast) 3282, 2948, 2925, 2905, 2854, 1470, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 1.02-1.17 (m, 1 H), 1.31-1.84 (m, 12 H), 3.45 (apparent dd, *J* = 10.6, 6.4 Hz, 1 H), 3.66 (dd, *J* = 10.5, 3.9 Hz, 1 H), 3.81 (t, *J* = 2.5 Hz, 1 H), 3.88 (q, *J* = 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.0 (q), -4.7 (q), 18.0 (s), 21.7 (t), 25.3 (t), 25.8 (q), 28.9 (t), 31.4 (t), 39.5 (d), 40.1 (d), 44.6 (d), 67.0 (t), 70.9 (d), 71.4 (d); exact mass *m/z* calcd for $C_{12}H_{23}O_3Si$ (M - C_4H_9) 243.14165, found 243.14165.

(3a*S*,4*R*,6*R*,7*R*,7a*R*)-7-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-6-[(methylsulfonyl)oxy]-1*H*-indene-4-yl]methyl Methanesulfonate (35.6).

35.5 **35.6**

Et_3N (1.50 mL, 1.08 mmol) was added into a stirred solution of **35.5** (0.9552 g, 3.179 mmol) in dry CH_2Cl_2 (60 mL). The solution was then cooled (ice bath), causing precipitation of **35.5**. $MeSO_2Cl$ (0.75 mL, 0.00969 mol) was added dropwise over *ca* 5 min, the mixture becoming homogeneous after the first few drops. The cold bath was removed after 3.5 h, and stirring was continued for a further 1.5 h. Evaporation of the solvent at room temperature, and flash chromatography of the residue over silica gel; using 3% *t*-BuOMe-CH_2Cl_2, gave crude **35.6**. This was again subjected to flash chromatography over silica gel, this time using 20% EtOAc-hexane, to give pure **35.6** (1.3692 g, 94%) as a viscous, colorless oil: FTIR (CH_2Cl_2, cast) 3464, 2954, 2917, 2849, 1356, 1177 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.04 (s, 3 H), 0.09 (s, 3 H), 0.88 (s, 9 H), 1.10-1.20 (m, 1 H), 1.37-1.47 (m, 2 H), 1.52-1.73 (m, 6 H), 1.80-1.90 (m, 2 H), 1.97 (dt, *J* = 14.2, 2.9 Hz, 1 H), 2.98 (s, 3 H), 3.01 (s, 3 H), 4.02 (dd, *J* = 9.8, 2.4 Hz, 1 H), 4.03 (br s, 1 H), 4.21 (dd, *J* =

9.6, 4.3 Hz, 1 H), 4.68 (q, J = 2.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ -5.1 (q), -4.8 (q), 17.9 (s), 21.4 (t), 25.1 (t), 25.7 (q), 28.4 (t), 29.2 (t), 37.4 (d), 37.6 (d), 38.46 (q), 38.53 (q), 44.5 (d), 68.5 (d), 72.3 (t), 79.6 (d); exact mass m/z calcd for $C_{14}H_{27}O_7SiS_2$ (M - C_4H_9) 399.09674, found 399.09645.

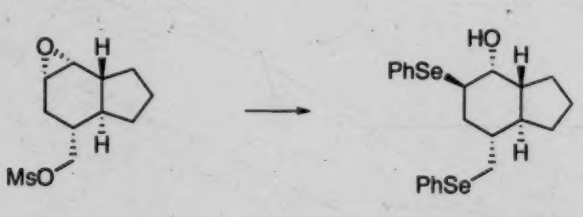
(1a*S*,3*R*,3a*S*,6a*R*,6b*R*)-[Octahydro-2*H*-indeno[4,5-*b*]oxirene-3-yl]methyl Methanesulfonate (37.2).

35.6 **37.2**

Bu_4NF (1.0 M in THF, 0.17 mL, 0.17 mmol) was injected in one portion by syringe into a stirred solution of **35.6** (0.0689 g, 0.151 mmol) in THF (5 mL). The mixture was stirred for 50 min and another portion of Bu_4NF (1.0 M in THF, 0.10 mL, 0.10 mmol) was added. After an additional 45 min, the mixture was taken up in EtOAc, and water was added. The aqueous layer was extracted twice with EtOAc, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 30% EtOAc-hexane, gave **37.2** (0.0295 g, 79%) as a solid: FTIR ($CDCl_3$, cast) 2917, 2870, 1352, 1175 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.10 (ddd, J = 10.5, 11.9, 8.1 Hz, 1 H), 1.32 (ddd, J = 11.6, 11.3, 6.4 Hz, 1 H), 1.46 (apparent dd, J = 10.5, 8.3 Hz, 1 H), 1.58-1.79 (m, 6 H), 1.83-1.90 (m, 1 H), 2.17 (dd, J = 4.9, 4.1 Hz, 1 H), 2.98 (s, 3 H), 3.17 (t, J = 4.3 Hz, 1 H), 3.26 (d, J = 4.1 Hz, 1 H), 3.94 (dd, J = 9.6, 6.9 Hz, 1 H), 4.14 (dd, J = 9.6, 4.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3 (t), 26.9 (t), 27.5 (t), 27.8 (t), 37.4 (q), 38.56 (d), 38.59 (d), 45.9 (d), 51.7 (d), 54.5 (d), 72.5 (t); exact mass m/z calcd for $C_{11}H_{18}NaO_4S$ (M + Na) 269.082351, found 269.082782.

Note: There is a competing reaction, and the R_f of the side product (TLC) is too similar to that of the **37.2** for reaction monitoring purposes. Experiments in which Bu_4NF was added until all **35.6** has disappeared (TLC control, variety of solvents) gave yields of 61% (reaction done at 0 °C), and 65% (room temperature). The reaction could probably be further optimized.

(3a*R*,4*R*,5*R*,7*R*,7a*R*)-Octahydro-5-(phenylseleno)-7-[(phenylseleno)-methyl]-1*H*-inden-4-ol (28.3).



37.2 **28.3**

$NaBH_4$ (375 mg, 9.92 mmol) was tipped in one portion (H_2 evolution!) into a stirred solution of PhSeSePh (1.47 g, 4.70 mmol) in dry, degassed MeOH, (20 mL) under N_2. The reaction flask was immediately resealed and flushed with N_2. A solution of **37.2** (284.1 mg, 1.115 mmol) in MeOH (5 mL, followed by 2 x 2 mL as a rinse) was added and the resulting clear, colorless solution was stirred for 40 h. Saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using first hexane until all yellow PhSeSePh was removed, and then 15% EtOAc-hexane, gave **28.3** (433.0 mg, 81%) as an oil: FTIR ($CDCl_3$, cast) 3405, 3069, 2951, 2869, 1578, 1477 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06-1.15 (m, 1 H), 1.37-1.66 (m, 6 H), 1.75-1.92 (m, 4 H), 2.16 (dt, *J* = 14.0, 2.6 Hz, 1 H), 2.73 (dd, *J* = 11.9, 8.7 Hz, 1 H), 3.15 (dd, *J* = 12.0, 3.4 Hz, 1 H), 3.58 (dt, *J* = 4.1, 2.6 Hz, 1 H), 4.12 (br s, 1 H), 7.20-7.26 (m, 6 H), 7.46-7.53 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz)

δ 21.3 (t), 25.8 (t), 29.0 (t), 32.7 (t), 33.9 (t), 40.1 (d), 43.3 (d), 45.4 (d), 48.6 (d), 70.6 (d), 126.6 (d), 127.4 (d), 128.9 (d), 129.1 (d), 130.1 (s), 130.9 (s), 132.7 (d), 133.8 (d); exact mass *m/z* calcd for $C_{22}H_{26}O^{80}Se_2$ 466.03140, found 466.03157.

(3a*R*,5*R*,7*R*,7a*R*)-Octahydro-5-(phenylseleno)-7-[(phenylseleno)methyl]-4*H*-inden-4-one (37.4).

28.3 **37.4**

Dess-Martin periodinane (36 mg, 0.085 mmol) was added in one portion into a stirred solution of **28.3** (16 mg, 0.035 mmol) in CH_2Cl_2 (5 mL). After 70 min, the reaction was quenched by addition of a mixture of saturated aqueous $NaHCO_3$ (1 mL) and aqueous $Na_2S_2O_3$ (1.0 M, 1 mL), as a byproduct had begun to form (TLC control, silica, 1:5 EtOAc-hexane). Stirring was continued for 1 h, and water (5 mL) was added. The mixture was extracted with three portions of CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 10% EtOAc-hexane, gave **37.4** (11.0 mg, 69%) as an oil: FTIR ($CHCl_3$, cast) 2958, 2872, 1706, 1577, 1477, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22-1.31 (m, 1 H), 1.42-1.76 (m, 5 H), 1.88 (apparent sextet of d, *J* = 6.2, 2.2 Hz, 1 H), 2.04 (apparent ddd, *J* = 11.8, 14.1, 5.1 Hz, 1 H), 2.08-2.16 (m, 1 H), 2.57 (ddd, *J* = 14.1, 2.9, 1.8 Hz, 1 H), 2.74 (dd, *J* = 12.2, 8.4 Hz, 1 H), 3.05 (dt, *J* = 12.7, 8.9 Hz, 1 H), 3.19 (dd, *J* = 12.2, 3.3 Hz, 1 H), 3.84 (dd, *J* = 5.2, 1.8 Hz, 1 H), 7.24-7.28 (m, 6 H), 7.48-7.53 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2 (t), 22.8 (t), 30.3 (t), 32.7 (t), 39.7 (d), 40.1 (t), 50.2 (d), 51.6 (d), 52.8 (d), 127.2 (d), 128.2

(d), 129.0 (d), 129.2 (s), 129.3 (s), 130.4 (s), 133.1 (d), 134.2 (d), 207.7 (s); exact mass *m/z* calcd for $C_{22}H_{24}O^{80}Se_2$ 464.01575, found 464.01662.

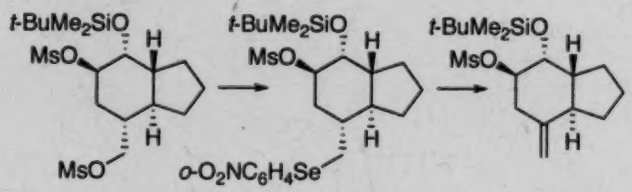
(3a*R*,7a*R*) 1,2,3,3a,7,7a-Hexahydro-7-methylene-4*H*-inden-4-one (28.1).

37.4 **28.1**

H_2O_2 (30% w/v, 0.30 mL, *ca* 3.5 mmol) was added into a stirred solution of **37.4** (59.0 mg, 0.128 mmol) in CH_2Cl_2 (10 mL). After 25 h, saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were dried ($MgSO_4$), and gently concentrated under water pump vacuum at room temperature, the flask being removed from the rotary evaporator 5 min after all solvent appeared to have evaporated. Flash chromatography of the residue over silica gel, using 1:10 EtOAc-hexane, gave an oil, the eluant being evaporated in the same careful manner as before. The oil was placed under oil pump vacuum for *ca* 1 min to give **28.1** (10.9 mg, 58%) as a volatile solid: mp 33-34 °C.

In a different experiment a sample of the oil was subjected to Kugelrohr distillation: oven temperature *ca* 170 °C: FTIR (CH_2Cl_2, cast) 2961, 2925, 2873, 2854, 1686, 1260, 1091, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.59-1.82 (m, 4H), 1.90-1.98 (m, 1 H), 2.0-2.06 (m, 1 H), 2.34-2.41 (m, 1 H), 2.50-2.59 (m, 1 H), 5.21 (apparent d of quintets, J = 2.9, 0.8 Hz, 1 H), 5.31 (apparent q, J = 1.0 Hz, 1 H), 5.94 (dd, J = 9.8, 0.6 Hz, 1 H), 7.03 (dq, J = 9.7, 0.7, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (t), 23.4 (t), 27.7 (t), 47.6 (d), 54.2 (d), 116.3 (t), 128.8 (d), 145.4 (s), 147.0 (d), 201.1 (s); exact mass *m/z* calcd for $C_{10}H_{12}O$ 148.08882, found 148.08903.

(3a*R*,4*R*,5*R*,7a*R*)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-7-methylene-1*H*-inden-5-yl Methanesulfonate, (38.3).



35.6 **38.2** **38.3**

$NaBH_4$ (68.8 mg, 1.82 mmol) was added in small portions over *ca* 5 min into a stirred solution of *o*-nitrophenylselenocyanate (0.250 g, 1.10 mmol) in dry MeOH (5 mL), and stirring was continued until the resulting suspension became deep red and homogeneous (*ca* 40 min). A solution of **35.6** (88.4 mg, 0.194 mmol) in MeOH (2.5 mL, followed by 2 x 1 mL as a rinse) was added by syringe, and the resulting solution was refluxed for 7 h. A yellow precipitate formed, and two portions of $NaBH_4$ (each *ca* 25 mg) were added 45 min and 3.5 h after reflux began. The solution was cooled to room temperature and evaporated. The residue was filtered through a small pad of silica gel, using EtOAc. Evaporation of the filtrate and flash chromatography of the residue over silica gel, using 20% EtOAc-hexane, gave crude **38.2**, which was used in the next step without further purification, and some starting dimesylate (**35.6**, 9.6 mg, 11%).

H_2O_2 (30% w/v, 0.20 mL, *ca* 2.3 mmol) was added into a stirred solution of the above crude selenide in THF (10 mL), and stirring was continued for 14 h. The mixture was then partitioned between Et_2O (10 mL) and water (10 mL), and the aqueous phase was extracted with Et_2O (1 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 10% EtOAc-hexane, gave **38.3** (35.9 mg, 51% over two steps). The yield of the product, corrected for recovered starting material, was 58%: FTIR (CH_2Cl_2, cast) 2955, 2857, 1472, 1360, 1259, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 3 H), 0.12 (s, 3 H), 0.89 (s, 9 H), 1.45-1.81 (m, 7 H),

2.22 (dt, J = 5.8, 11.7 Hz, 1 H), 2.43 (dd, J = 14.8, 2.7 Hz, 1 H), 2.56 (d of sextets, J = 14.8, 1.9 Hz, 1 H), 3.0 (s, 3 H), 4.07 (br s, 1 H), 4.68 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -5.0 (q), -4.6 (q), 18.0 (s), 21.2 (t), 25.5 (t), 25.8 (q), 26.1 (t), 35.6 (t), 38.8 (q), 42.3 (d), 46.3 (d), 68.9 (d), 80.7 (d), 107.0 (t), 145.7 (s); exact mass m/z calcd for $C_{17}H_{32}O_4SiS$ 360.17905, found 360.17836.

(1,1-Dimethylethyl)dimethyl[[(3a*R*,4*R*,7a*R*)-2,3,3a,4,7,7a-hexahydro-7-methylene-1*H*-inden-4-yl]oxy]silane (38.4).

38.3 **38.4**

DBU (0.08 mL, 0.535 mmol) was injected into a stirred solution of **38.3** (35.9 mg, 0.0997 mmol) in dry, distilled *o*-xylene (5 mL). The mixture was refluxed for 10 h, giving the elimination product. Because the product is volatile and of low polarity it is not practical to separate it from the reaction solvent (3 days reflux in toluene gives no observed conversion), and so the solution was used directly in the next step.

(3aR,4R,7aR)-2,3,3a,4,7,7a-Hexahydro-7-methylene-1*H*-inden-4-ol (38.5).

38.4 **38.5**

When the above solution had cooled to room temperature, THF (5 mL) and then Bu_4NF (1.0 M in THF, 0.60 mL, 0.60 mmol) were added. Stirring was continued for 24 h,

and the solution was diluted with EtOAc (25 mL) and washed with saturated aqueous NH_4Cl, water and brine. The organic extract was dried ($MgSO_4$) and carefully evaporated under water pump vacuum until *ca* 1 mL of solvent remained. This solution was filtered through a column of flash chromatography silica gel made up with hexane, and the product was eluted with CH_2Cl_2. Evaporation of the filtrate and flash chromatography of the residue over silica gel, using 10% EtOAc-hexane, gave **38.5** (11.8 mg, 79% over 2 steps) as a white solid: mp = 69-71 °C: FTIR (CH_2Cl_2, cast) 3301, 3177, 2957, 2907, 2869, 1180, 1142, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22 (br s, 1 H), 1.44-1.56 (m, 2 H), 1.66-1.77 (m, 4 H), 1.99-2.05 (m, 1 H), 2.22-2.28 (m, 1 H), 4.20 (dd, *J* = 4.6, 4.1 Hz, 1 H), 4.88 (apparent dq, *J* = 3.7, 2.0 Hz, 1 H), 4.92 (br s, 1 H), 5.95 (dd, *J* = 9.5, 5.3 Hz, 1 H), 6.23 (dd, *J* = 9.6, 0.6 Hz, 1 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 22.5 (t), 25.3 (t), 27.6 (t), 40.1 (d), 48.1 (d), 64.8 (d), 110.9 (t), 130.9 (d), 132.5 (d), 147.6 (s); exact mass *m/z* calcd for $C_{10}H_{14}O$ 150.10446, found 150.10469.

(3a*R*,7a*R*) 1,2,3,3a,7,7a-Hexahydro-7-methylene-4*H*-inden-4-one (28.1).

38.5 **28.1**

Dess-Martin periodinane (85.5 mg, 0.202 mmol) was tipped in one portion into a stirred solution of **38.5** (19.2 mg, 0.128 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 2 h (TLC control, silica, 20% EtOAc-hexane) and a solution of $Na_2S_2O_3$ (285 mg, 1.80 mmol) in saturated aqueous $NaHCO_3$ (1 mL) was added. The resulting mixture was stirred for 10 min, diluted with water (5 mL), and extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 1:10 EtOAc-hexane, gave **28.1** (17.0 mg, 90%).

(3a*R*,4*S*,7a*R*) 2,3,3a,4,7,7a-Hexahydro-7-methylene-1*H*-inden-4-ol (39.2).

28.1 **39.2**

$CeCl_3 \cdot 7H_2O$ (20.1 mg, 0.0539 mmol) was added quickly into a stirred solution of **28.1** (6.6 mg, 0.044 mmol) in dry MeOH (2 mL) at -20 °C. After 10 min, $NaBH_4$ (3.4 mg, 0.089 mmol) was added in one portion, and the mixture was stirred for a further 10 min. Water (1 mL) and brine (5 mL) were added, and the solution was extracted with $CHCl_3$ (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to afford clear, white crystals, mp = 125-127 °C. The ^1H NMR spectrum showed alcohol **39.2** contaminated with alcohol **38.5**. The major product (**39.2**) had: FTIR ($CHCl_3$, cast) 3321, 2956, 2881, 2865 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.32-1.41 (m, 1 H), 1.44-1.56 (m, 3 H), 1.68-1.82 (m, 2 H), 1.95-2.02 (m, 1 H), 2.06-2.14 (m, 2 H), 4.16 (d, *J* = 9.1 Hz, 1 H), 4.78 (s, 1 H), 4.88 (s, 1 H), 5.71 (d, *J* = 9.8 Hz, 1 H), 6.13 (dd, *J* = 9.7, 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.3 (t), 27.5 (t), 29.2 (t), 45.6 (d), 51.8 (d), 74.6 (d), 109.9 (t), 131.0 (d), 133.8 (d), 146.4 (s); exact mass *m/z* calcd for $C_{10}H_{14}O$ 150.10422, found 150.10446.

6 REFERENCES AND FOOTNOTES

1 Jordan, M. A.; Wilson, L. *Curr. Opin. Cell Biol.* **1998**, *10*, 123.

2 (a) Hamel, E. *Biopolymers (Pept. Sci.)* **2002**, *66*, 142. (b) Hamel, E.; Covell, D. G. *Curr. Med. Chem. Anti-Cancer Agents* **2002**, *2*, 19.

3 Cragg, G. M.; Newman, D. J. *J. Nat Prod*, **2004**, 67, 232.

4 (a) Jordan, M. A.; Toso, R. J.; Thrower, D.; Wilson, L. *Proc. Natl. Acad. Sci. USA*

1993, *90*, 9552. (b) Dhamodharan, R.; Jordan, M. A.; Thrower, D.; Wilson, L.; Wadsworth, L. *Mol. Biol. Cell.* **1995**, *6*, 1215.

5 Rowinsky, E. K. *Ann. Rev. Med.* **1997**, *48*, 353.

6 Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325.

7 Rowinsky, E. K.; Donehower, R. C. *Pharmacol. Ther.* **1991**, *52*, 35.

8 Hastie, S. B. *Pharmacol. Ther.* **1991**, *51*, 377.

9 Kuriyama, R.; Sakai, H. *J. Biochem. (Tokyo)*, **1974**, *76*, 651.

10 Combeau, C.; Provost, J.; Lancelin, F.; Tournoux, Y.; Prod'homme, F.; Herman, F.; Lavelle, F.; Leboul, J.; Vuilhorgne, M. *Molecular Pharmacology* **2000**, *57*, 553.

11 Bai, R.; Lin, C. M.; Nguyen, N. Y.; Liu, T.-Y.; Hamel, E. *Biochemistry* **1989**, *28*, 5606.

12 Shan, B.; Medina, J. C.; Santha, E.; Frankmoelle, W. P.; Chou, T-C.; Learned, R. M.; Narbut, M. R.; Stott, D.; Wu, P.; Jaen, J. C.; Timmermans, P. B. M. W. M.; Beckmann, H. *Proc. Natl. Acad. Sci. USA*, **1999**, *96*, 5686.

13 Legault, J.; Gaulin, J.-F.; Mounetou, E.; Bolduc, S.; Lacroix, J.; Poyet, P.; C.-Gaudreault, R. *Cancer Res.* **2000**, *60*, 985.

14 As quoted in reference #15: Li, H.; Li. H; Qu, X.; Shi, Y.; Guo, L.; Yuan, Z. *Zhongguo Zhongyao Zazhi (Chin. J. Chin. Mater. Med.)* **1995**, *20*, 115, 128.

15 Ayyad, S-E. N.; Judd, A. S.; Shier, W. T.; Hoye, R. T. *J. Org. Chem.* **1998**, *63*, 8102.

16 Levoul, J.; Provost, J. World Patent WO96/00205, 1996.

17 Mehta, G.; Reddy, D. S. *J. Chem. Soc., Chem. Commun.* **1999**, 2193.

18 Mehta, G.; Islam, K. *Synlett*, **2000**, 1473.

19 Mehta, G.; Islam, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 2396.

20 Mehta, G., Islam, K. *Tetrahedron Lett.* **2003**, *44*, 6733.

21 Araki, H.; Inoue, M.; Katoh, T. *Org. Lett.* **2003**, *5*, 3903.

22 E.g. (a) Cicero, B. L.; Weisbuch, F.; Dana, G. *J. Org. Chem.*, **1981**, *46*, 914. (b) Kobayashi, M.; Yasuzawa, T.; Kyogoku, Y.; Kido, M.; Kitagawa, I. *Chem. Pharm. Bull. Jpn.* **1982**, *30*, 3431. (c) Paquette, L. A.; Romine, J. L.; Lin, H.-S.; Wright, J. *J. Am. Chem. Soc.*, **1990**, 112, 9284. (d) Doyen, J.; He, W.; Paquette, L. A. *J. Org. Chem.*, **1994**, *59*, 2033.

23 House, H. O.; Rasmussen, G. H. *J. Org. Chem.*, **1963**, *28*, 31.

24 Trembleau, L.; Patiny, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 6377.

25 Mehta, G.; Islam, K. *Org. Lett.* **2002**, *4*, 2881.

26 Araki, H.; Inoue, M.; Katoh, T. *Synlett*, **2003**, 2401.

27 Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.

28 Izuhara, T.; Katoh, T. *Tetrahedron Lett.* **2000**, *41*, 7651.

29 Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443.

30 See footnote 18 in reference 21.

31 (a) Restrepo-Sánchez, N. E.; Gómez, F. J.; Jaramillo-Gómez, L. M.; Hudlicky, T. *Synth. Commun.* **1999**, *29*, 2795. (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71. (c) Margot, C.; Schlosser, M. *Tetrahedron Lett.* **1985**, *26*, 1035.

32 Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582.

33 We thank Professor K. Narasaka for experimental advice on the preparation of **30.2**.

34 Evans, D. A.; Petersen, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.*, **1998**, *63*, 4541.

35 *Cf.* (a) Sanseverino, A. M.; de Mattos, M. C. S. *Synthesis*, **1998**, 1584. (b) Cambie, R. C.; Noall, W. I.; Potter, G. J.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1*, **1977**, 226.

36 Discussion of π-facial selectivity in electrophilic reactions of unsaturated alcohols and acids: Chamberlin, A. R.; Mulholland Jr., R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.*, **1987**, *109*, 672.

37 *Cf.* (a) Barrett, A. G. M.; Rys, D. J. *J. Chem. Soc., Chem. Commun.* **1994**, 837. (b) Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271.

38 With the triflate, attempted displacement with PhSe- in methanol provided mostly the methanol displacement derivative. Use of other procedures to generate the selenoxide anion gave complex mixtures.

39 We thank Professor M. Klobukowski for performing the calculations.

40 Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

41 Clive, D. L. J.; Fletcher, S. P. *J. Chem. Soc., Chem. Commun.* **2002**, 1940.

42 Doyon, J.; He, W.; Paquette, L. A. *J. Org. Chem.* **1994**, *59*, 2033.

43 *Cf.* (a) Arjona, O.; Pradilla, R. F.; Mallo, A.; Perez, S.; Plumet, J. *J. Org. Chem.* **1989**, *54*, 4158. (b) Arjona, O.; Pradilla, R. F.; Martin-Domenech, A.; Plumet, J. *Tetrahedron*, **1990**, *46*, 8187.

44 (a) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061. (b) Roush, W. R.; Gilles, H. R.; Vo, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269.

CHAPTER II
FORMAL RADICAL CYCLIZATION ONTO A BENZENE RING: FORMATION OF BENZO-FUSED OXYGEN HETEROCYCLES, SYNTHESIS OF NOCARDIONE A, AND FORMATION OF BENZO-FUSED NITROGEN HETEROCYCLES

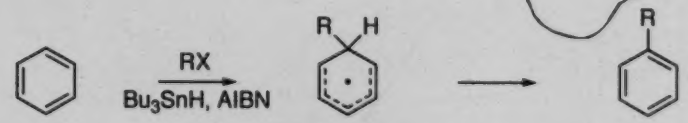
1 INTRODUCTION

1.1 Background

Radical cyclization onto a double bond is now a standard synthetic method. The corresponding cyclizations onto an aromatic ring would be useful, but the process is rare, and most radical additions to benzene rings are inefficient and require large amounts of initiator.

1.1.1 Mechanistic Considerations

When a radical adds to a benzene ring under normal stannane-mediated conditions, a cyclohexadienyl radical is generated. The radical is stabilized through resonance with the adjacent π-system and is reluctant to propagate the radical chain by hydrogen abstraction from the stannane (Scheme 1). Typically, the cyclohexadienyl radical undergoes rearomatization to a substituted benzene ring, but the mechanism for this process is the subject of debate. It is often assumed that a regioisomeric mixture of cyclohexadienes is formed which undergoes oxidation to the arene. However, cyclohexadienes are easy to form – and isolate - through Birch type reductions, and so cyclohexadiene oxidation is probably not a significant pathway.



Scheme 1

When a propagation step in a radical chain is inefficient there is a buildup of radical concentration and an increase in the chance of radical-radical reactions. The formation of dimerization or disproportionation products also has the effect of removing radicals from the chain. In such circumstances, if the substrate is to be fully consumed, while radicals are being removed from the chain, a large amount of chain initiator is required. The tin-hydride

mediated addition of radicals to benzene rings requires a disproportionately large amount of AIBN as radical initiator.

Curran has suggested that the need for an excess of initiator may be due to oxidation of the cyclohexadienyl radicals by the initiator, or by an initiator-derived radical.[1] Conversely, Bowman has proposed several mechanistic variations which involve deprotonation of the cyclohexadienyl radical by stannane, so producing a radical anion, Bu_3Sn^+, and molecular hydrogen (equation 1).[2] The radical anion would then undergo one of several processes to give an aromatic product.

(1) $$ArRH\bullet + Bu_3SnH \rightarrow [Ar\text{-}R]\bullet^- + Bu_3Sn^+ + H_2$$

These mechanisms are subject to debate and, until very recently, were not at all well understood.[3] Recent detailed mechanistic studies from the Bowman laboratory have ruled out mechanisms involving Equation 1. It appears that the predominant reaction sequence involves the initiator acting as an oxidizing agent, in the sense shown in Equation 2, but the exact details remain unclear.[4]

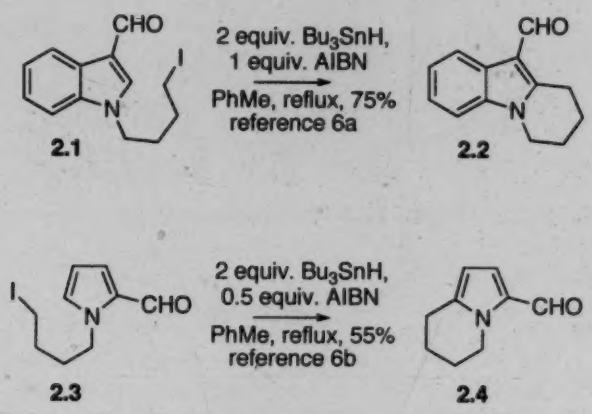
(2) $$2ArRH\bullet + R'\text{-}N{=}N\text{-}R' \rightarrow 2Ar\text{-}R + R'NHNHR'$$

The same mechanistic considerations probably apply to alternative hydride sources such as tris(trimethylsilyl)silane and Bu_3GeH.[4]

1.1.2 Radical Cyclization onto Heteroaromatic Rings

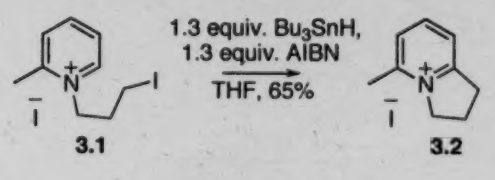
Radical cyclization onto aromatic heterocycles is a reasonably well-known process.[5] Radicals may be "oxidatively" cyclized onto pyrroles, indoles and imidazoles that contain electron-withdrawing groups. Typical examples are shown in Scheme 2.[6] It appears that

electron withdrawing groups are necessary for this process to be successful, and even then yields can be modest.



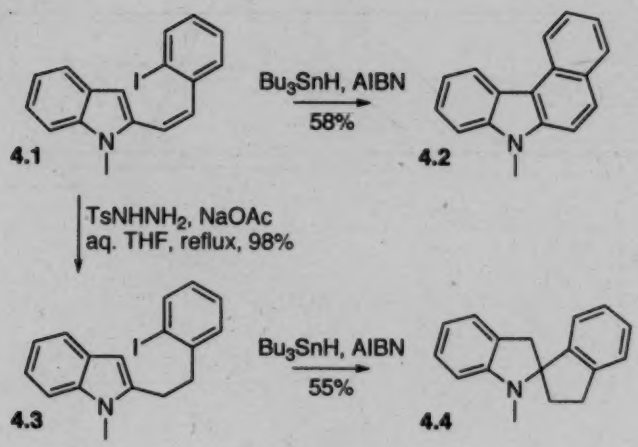
Scheme 2

In the presence of π-radical stabilizing groups, oxidative radical cyclization onto indoles,[7] pyridines,[8] 1,2,3-triazoles,[9] pyridones,[10] and pyrazoles[11] may also be accomplished. Electron deficient pyridinium salts (Scheme 3) undergo radical cyclization efficiently when an excess of AIBN is used and the stannane is added in one portion.[12]



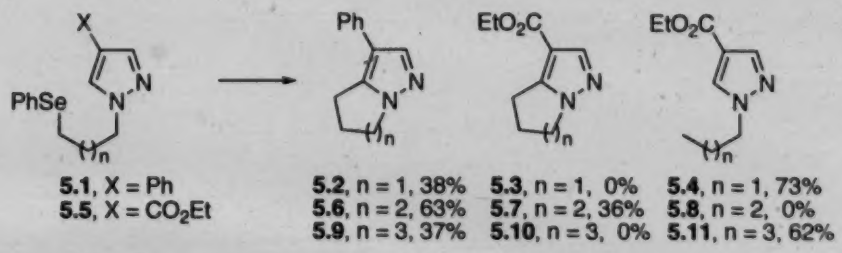
Scheme 3

These radical cyclization processes may be manipulated to control the reaction pathway, and an example is shown in Scheme 4.[7a] In this case reductive spirocyclization may occur at C-2 of the indole ring or oxidative cyclization may occur at C-3, depending on the presence or absence of a double bond in the connecting chain.



Scheme 4

The above processes work in good yields. However these reactions are often not general, as illustrated in Scheme 5. Stannane-mediated cyclization of **5.1** (X = Ph, n = 1), using 1.5 equivalents of radical initiator, occurs in 38% yield to give the natural product withasomnine (**5.2**).[11] However, if X = CO_2Et (**5.5**, n = 1) the reaction gave the simple reduction product **5.4** and no cyclized material (**5.3**). For the six-membered homologues, **5.6** (X = Ph) was found to form in 63% yield, while when X = CO_2Me only 36% of the desired cyclized product (**5.7**) formed, and no simple reduction product (**5.8**) was found. In the case of seven-membered ring formation, if the value of X is Ph, the oxidatively cyclized product **5.9** could be obtained, but in low yield (37%). Reduction of **5.5** (n = 3) again gave no cyclized product (**5.10**) and the simple reduction product **5.11** was obtained (62%).



5.1, X = Ph
5.5, X = CO_2Et

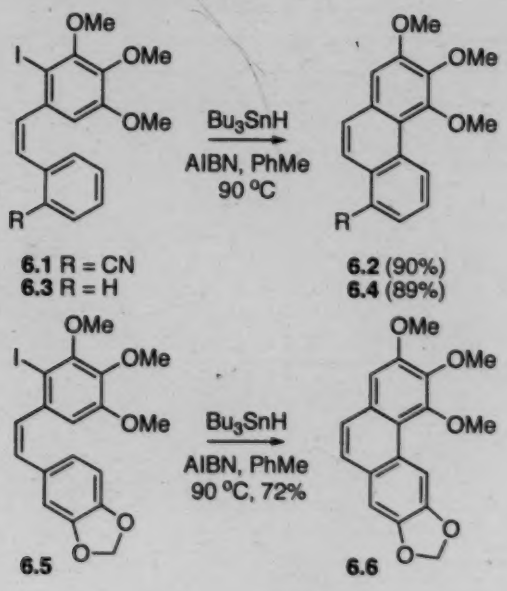
5.2, n = 1, 38% **5.3**, n = 1, 0% **5.4**, n = 1, 73%
5.6, n = 2, 63% **5.7**, n = 2, 36% **5.8**, n = 2, 0%
5.9, n = 3, 37% **5.10**, n = 3, 0% **5.11**, n = 3, 62%

Scheme 5

1.1.3 Attack on a Benzene Ring using Standard Radical Cyclization Conditions

(a) Formation of Polyaromatic Products

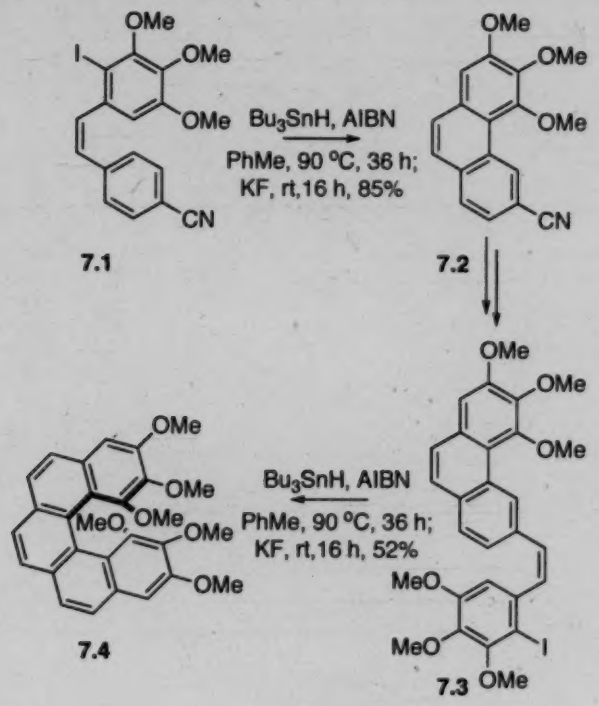
Polyaromatic products may be formed by radical cyclization of an electron rich aryl radical onto an electro-neutral, electron-rich or electron-poor arene. These cyclizations follow an oxidative radical pathway. Presumably, the formation of an extended π-network thermodynamically facilitates rearomatization. The ring may also be in a conformation that assists attack onto the aromatic nucleus. The authors of the examples shown in Scheme 6 did not report the amount of radical initiator used.[13]



Scheme 6

Typically, the use of *meta*-substituted aromatics leads to statistical mixtures of isomers, but cyclization of **6.5** provided **6.6** as the major product (72% yield). The origin of this selectivity is not clear, but was exploited in a synthesis of helicene **7.4** by the iterative radical cyclizations shown in Scheme 7. Treatment of *cis*-stilbene **7.3** with Bu_3SnH and an unreported amount of radical initiator gave **7.4** in 52% yield. Formation of the strained **7.4** was accompanied by a small amount (17%) of a more-linear isomer. The authors suggest

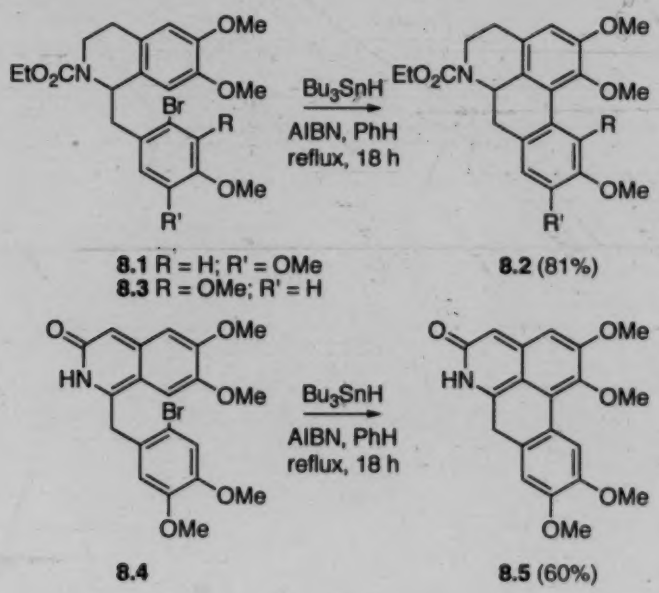
that this selectivity reflects a more favorable SOMO-LUMO interaction that leads to **7.4**. The radical intermediate cyclizes to give a major product that is clearly strained and this fact suggests that these cyclizations, and the subsequent loss of hydrogen to provide the aromatic product, are irreversible processes.[14]



Scheme 7

The synthesis of biaryls can also be accomplished using standard stannane methods. Conversion of benzylisoquinoline **8.1** into aporphine **8.2** was accomplished in 81% yield using nearly stoichiometric AIBN (Scheme 8).[15] Cyclization is often not observed when slight changes in the structure of the starting material are made. If the nitrogen atom is unprotected, rupture of the doubly benzylic carbon-carbon bond occurs. Treatment of **8.3** under the same conditions resulted in hydrogenolysis of the C-Br bond and no cyclization took place.

The conformation required for cyclization may be restricted by steric interactions between substituents on the two aromatic rings of **8.3**. However, the strained polycyclic aromatic helicene **7.4** (Scheme 7) formed readily. These observations suggest that a combination of subtle electronic differences and steric effects determine the success or failure of such cyclizations. Some structural variation, as seen in **8.4** → **8.5**, is tolerated.



8.1 R = H; R' = OMe
8.3 R = OMe; R' = H

8.2 (81%)

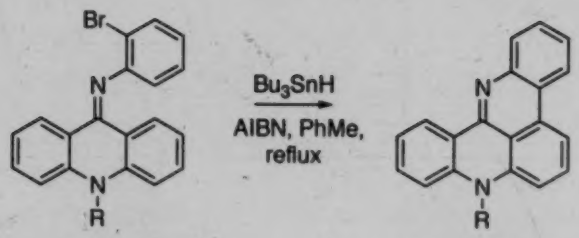
8.4

8.5 (60%)

Scheme 8

Polycyclic acridines are available (*cf.* Scheme 9), using tin hydrides and 10 mol% AIBN in refluxing PhMe. Free amines were not tolerated in this reaction. Typical examples are shown in Scheme 9. The reverse process, where the radical is generated on the acridine ring, also works well.[16]

Aryl radicals generated from *o*-bromobenzyl ethers do not readily provide benzopyrans, but some exceptions are shown in Scheme 10, and it is apparent that simple

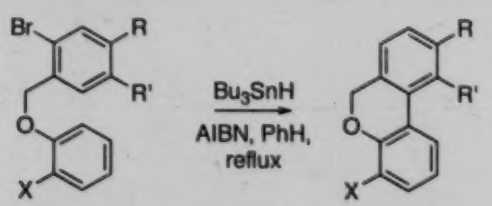


9.1 R = Me
9.3 R = Et
9.5 R = *i*-Pr

9.2 (69%)
9.4 (79%)
9.6 (54%)

Scheme 9

benzene rings (**10.1** → **10.2**, 48%) work well. Electron-donating groups on the ring bearing the aryl radical (**10.3** → **10.4**) are also tolerated. Substitution of the benzene ring accepting the radical is not tolerated, except in the case of an *ortho* ester moiety (**10.5** → **10.6**, 30%). It is suggested that the poor yields are due to reversibility of the initial radical reaction.[17] The conditions used for the cyclizations involved 1-2 equiv. of stannane, and 0.5-0.6 equivalents of AIBN in refluxing PhH.

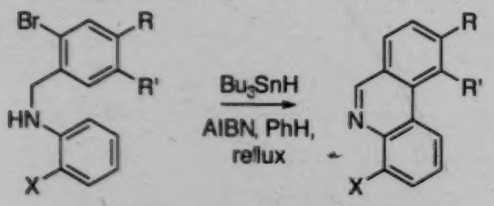


10.1 R = R' = H; X = H — **10.2** (48%)
10.3 R, R' = OCH_2O; X = H — **10.4** (47%)
10.5 R, R' = OCH_2O; X = CO_2Me — **10.6** (30%)

Scheme 10

Bowman *et al.* have studied the radical cyclization of *o*-bromobenzyl ethers and related compounds, and found similar results - an array of products arising though various rearrangement processes. Using a different halogen atom as the radical trigger did not improve the results.[20]

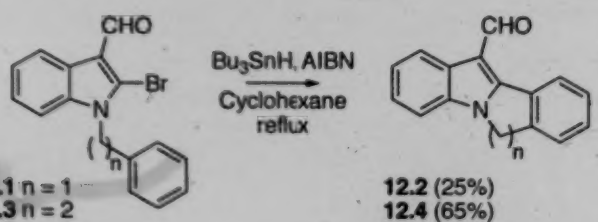
The nitrogen equivalent of the transformations shown in Scheme 10 is higher yielding (Scheme 11), as the process is facilitated by resonance stabilization provided by the amine moiety. The initial radical product undergoes double oxidation to a fully aromatic system. A variety of substitution patterns are tolerated.[18]



11.1 R, R' = OCH_2O; X = H **11.2** (66%)
11.3 R, R' = OCH_2O; X = OMe **11.4** (63%)

Scheme 11

A radical generated from substituted indole rings can add intramolecularly to unsubstituted benzene rings.[19] Yields are dependent on the length of the connecting carbon chain. Cyclohexane is used as the reaction solvent to avoid competitive addition with aromatic solvents. The amount of AIBN used in these reactions was not reported.[19]



12.1 n = 1 **12.2** (25%)
12.3 n = 2 **12.4** (65%)
12.5 n = 3 **12.6** (37%)
12.7 n = 4 **12.8** (0%)

Scheme 12

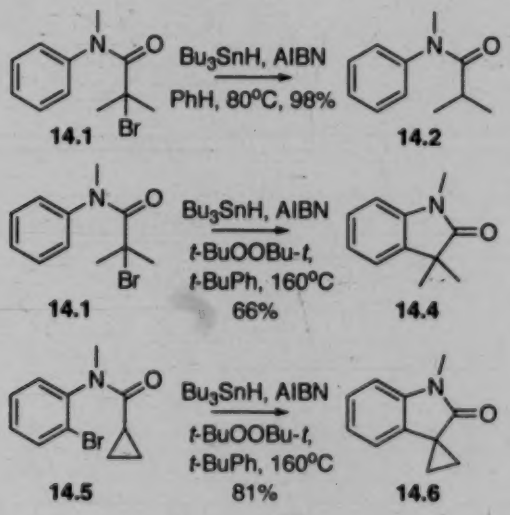
A class of cascade radical annulations is known to produce polycyclic systems (Scheme 13). The imidoyl radicals **13.1**, or their synthetic equivalents, can be produced by a variety of methods and give a variety of fusedquinolines **13.2**.[20]

13.1 13.2

Scheme 13

(b) Examples of non-Polyaromatic Products

Beckwith and Storey heated **14.1** at 80 °C with Bu_3SnH and an unreported amount of AIBN. This experiment provided the reduced compound **14.2** (98% yield by GC analysis).[21] When **14.1** and 0.1 M Bu_3SnH in *tert*-butylbenzene was heated at 160 °C, while catalytic amounts of di-*tert*-butyl peroxide were added in small portions over 4 hours, the cyclized product **14.4** was obtained in 66% yield. Reducing the effective concentration of tin hydride by slow addition of a mixture of stannane and di-*tert*-butyl peroxide at 160 °C was found to further improve the cyclization yields.



14.1 14.2 14.1 14.4 14.5 14.6

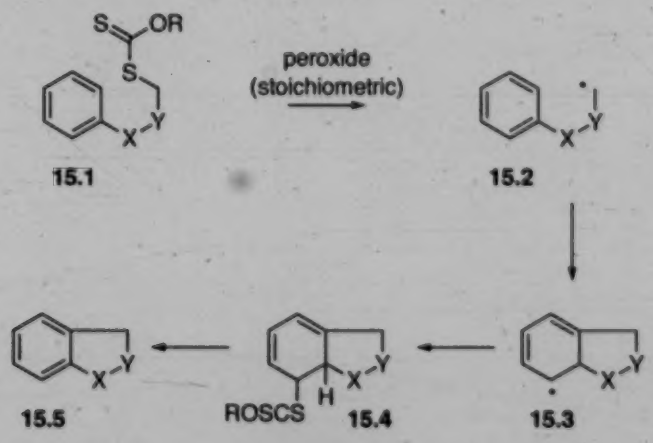
Scheme 14

This methodology is limited by the harsh reaction conditions, but has been applied to a tandem process involving radical translocation and then aromatic substitution. This process readily provides spiro-oxindoles, such as **14.6**, from aryl bromides.

Examples of radical cyclization onto a benzene ring to form a product that is not polyaromatic (such as the cases shown in Scheme 14) are rare, but another example is shown below (Scheme 21), where it is discussed in more detail. The radical is generated from a xanthate using a stannane and one equivalent of radical initiator to assist with the final aromatization. This particular reaction appears to be a unique version (use of a stannane instead of a peroxide) of the xanthate method, which is discussed in Section 1.1.4. The reaction provided a 6:4 mixture of two isomers in a combined yield of 60%.

1.1.4 Application of the Xanthate Method

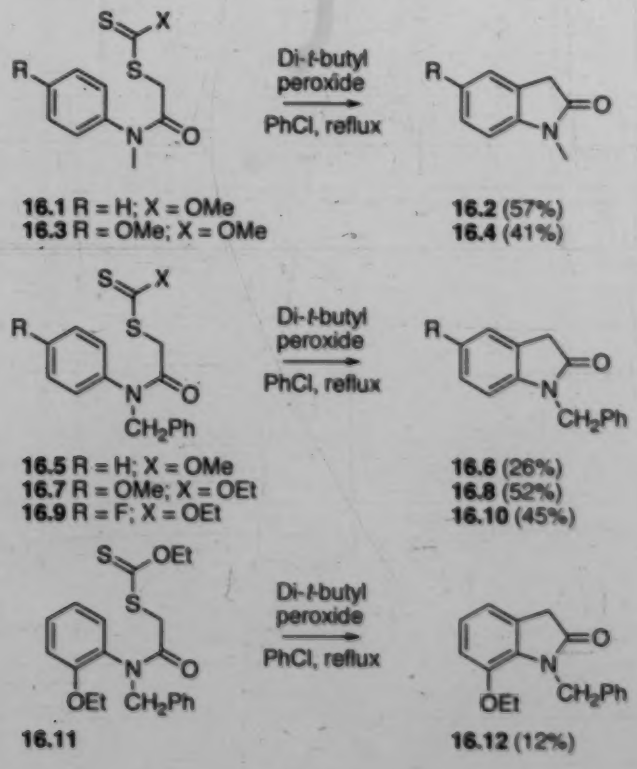
Zard *et al.* have published a series of papers reporting direct radical cyclization onto an aromatic ring. In these publications a xanthate[22] is used as the radical precursor. The conditions used strongly favor oxidative rearomatization over competing pathways. Another factor facilitating this process is that the xanthate (**15.1**) and its derived radical (**15.2**) exist in equilibrium; if they react with each other they produce **15.1** and **15.2** again.



Scheme 15

This process is proposed to generate the radical intermediate reversibly, a situation which gives the radical a long lifetime – sufficient, in fact, to overcome conformational factors slowing attack and facilitating the relatively slow ring-closure onto an aromatic ring (**15.2** → **15.3**). Radical **15.3** is too stabilized to propagate a chain reaction and so its formation is followed by oxidation through reaction with peroxide (**15.3** → **15.5**), or addition of xanthate (**15.3** → **15.4**), followed by aromatization to **15.5**.[23]

Limits to this methodology include use of stoichiometric peroxide and high reaction temperatures. These factors are incompatible with sensitive functional groups. Special care must also be taken to monitor the reaction, as excess peroxide tends to destroy the product once the starting xanthate has been depleted.[24] These conditions do allow halogen substituents, which would be reduced if stannanes or silanes were used.



16.1 R = H; X = OMe
16.3 R = OMe; X = OMe

16.2 (57%)
16.4 (41%)

16.5 R = H; X = OMe
16.7 R = OMe; X = OEt
16.9 R = F; X = OEt

16.6 (26%)
16.8 (52%)
16.10 (45%)

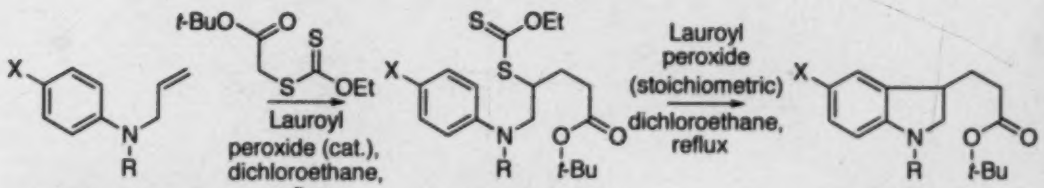
16.11

16.12 (12%)

Scheme 16

The xanthate method is limited to *para*-substituted arenes. *Meta*-substitution leads to a statistical mixture of regioisomers.[25a] The use of *ortho*-substituted derivatives in this method is complicated by *ipso*-substitution and complex mixtures are obtained.[25a]

The utility of this methodology is increased by a process allowing generation of the xanthate precursor by intramolecular radical addition (Scheme 17).[25] The intermolecular radical addition of a xanthate involves a radical chain, requiring only a catalytic amount of peroxide as initiator, while the radical cyclization process requires a stoichiometric amount.[25]



17.1 X = F; R = Ms
17.4 X = Br; R = Ms
17.7 X = OMe; R= Ms
17.10 X= H; R = Ac

17.2 (81%)
17.5 (83%)
17.8 (83%)
17.11 (57%)

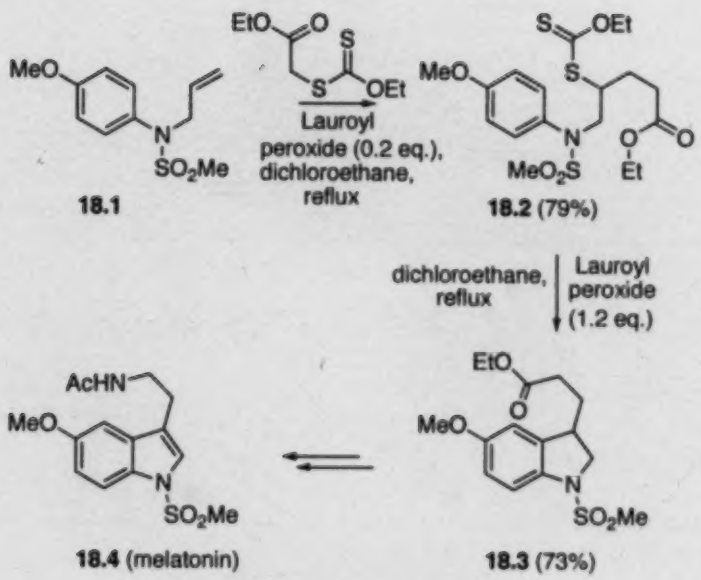
17.3 (79%)
17.6 (76%)
17.9 (70%)
17.12 (70%)

Scheme 17

The yields of the cyclizations summarized in Scheme 17 are higher than those in Scheme 16. Possibly, this is due to an electron withdrawing substituent on the nitrogen attached to the aromatic ring as well as the use of lauroyl peroxide.

The xanthate method has been applied to the synthesis of melatonin (**18.4**) (Scheme 18).[26] Addition of a xanthate to olefin **18.1**, mediated by portionwise addition of lauroyl peroxide, provided adduct **18.2** in 79% yield, and exposure of this compound to peroxide in refluxing 1,2-dichloroethane gave the ring closed indoline **18.3**.

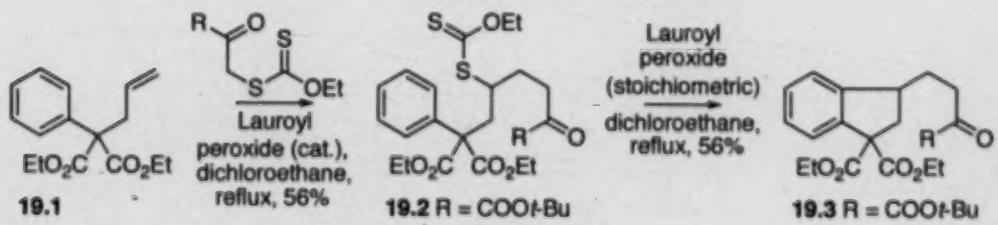
Extension of this approach to indanes provided mixed results, the highest yielding example is shown in Scheme 19. It appears that the geminal diester group is necessary for acceptable yields.[25]



Scheme 18

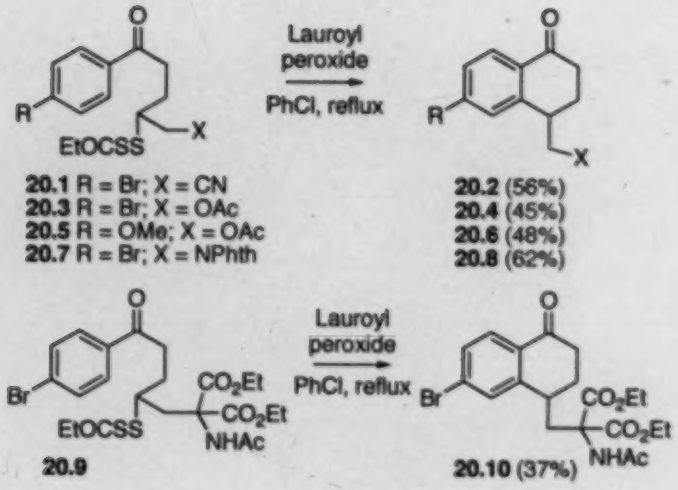
Various tetralones are available using this chemistry (Scheme 20).[24]

As shown in Scheme 21, tetrahydroisoquinolines are also available (*cf.* **21.1** → **21.2**), and yields are in the range of 46-63%.[25b] A variation of this method has been



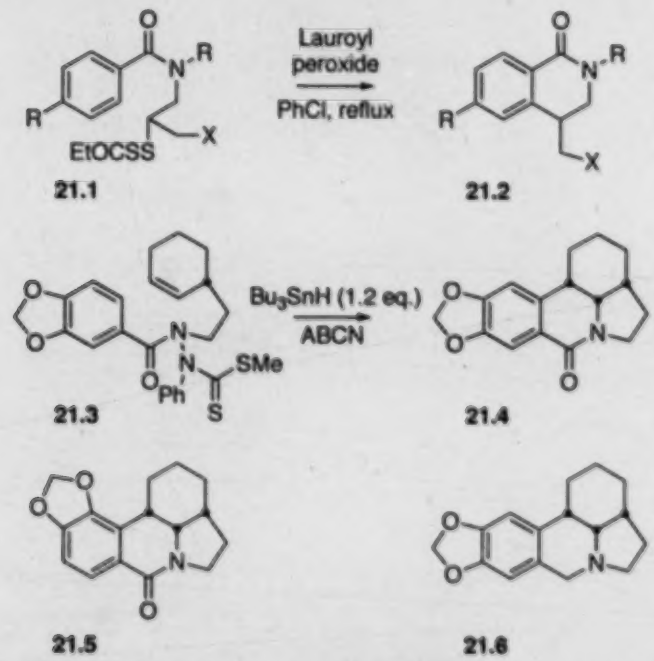
Scheme 19

applied to the synthesis of (±)-γ-lycorane (**21.6**), where an amidyl radical (generated from **21.3**) begins a radical cascade involving closure onto an olefin, and then onto an aromatic ring. Conditions to generate the radical involve a stannane and an equivalent of initiator rather than a peroxide.



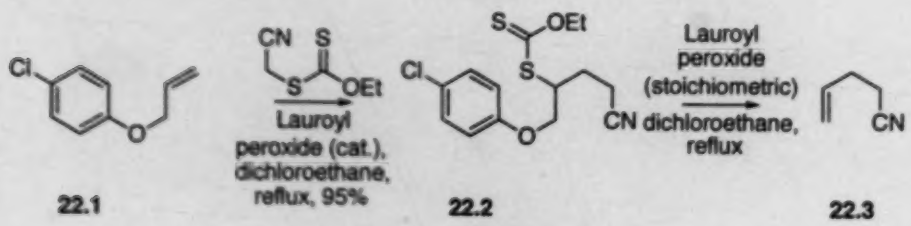
Scheme 20

The reaction provided a 6:4 mixture of **21.4** and its isomer **21.5**, in 60% combined yield.[27] The conversion of **21.4** to γ-lycorane (**21.6**) was previously described.



Scheme 21

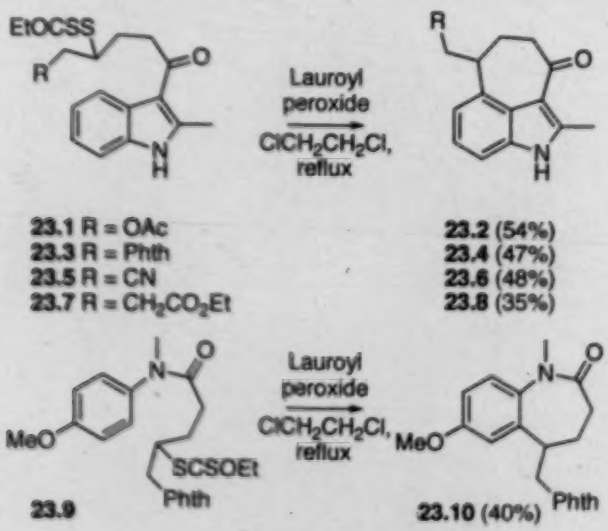
Dihydrobenzofurans are not available using this approach.[25] Addition of a xanthate to *O*-allyl *p*-chlorophenol **22.1** was efficient (95%, Scheme 22), but radical cyclization of **22.2** was not observed under the usual conditions employed by Zard. The oxidative conditions generated a radical which expelled a *p*-chlorophenoxy radical, and provided *p*-chlorophenol and nitrile **22.3**.[25]



22.1 **22.2** **22.3**

Scheme 22

The xanthate method has also recently been applied to seven-membered rings. Yields are in the range of 26-54%, and typical examples are shown in Scheme 23.[28] Seven-membered rings can also be formed by stannane-mediated radical addition onto certain



23.1 R = OAc
23.3 R = Phth
23.5 R = CN
23.7 R = CH_2CO_2Et

23.2 (54%)
23.4 (47%)
23.6 (48%)
23.8 (35%)

23.9

23.10 (40%)

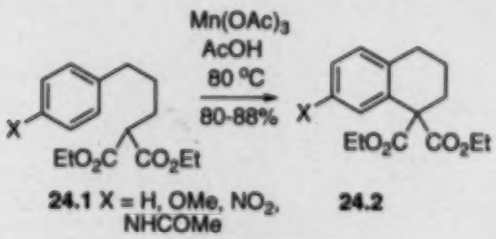
Scheme 23

aromatic nuclei. Examples involve pyrrole or imidazole heteroaromatics that are activated by an electron-withdrawing group. The photolysis of chloroamides has also been used to form seven-membered rings, but yields are modest and the photolysis may involve single electron transfer rather than neutral radical intermediates.[29]

1.1.5 Cyclizations of Radicals from β-Dicarbonyl Compounds

Free-radical cyclization can be applied to benzene rings when the initial radical is generated oxidatively, and the radical product is terminated oxidatively.[30] This large subject has been reviewed.[30] In this case there is no radical chain that can be adversely affected by the considerations discussed in Section 1.1.1.

In the case of β-dicarbonyl compounds, a proton is lost and the resulting anion is oxidized by a metal to generate a radical. An advantage of this strategy is that the radical precursor is simple and usually readily available. Disadvantages include the use of excess oxidant, the fact that the product often possess potentially unwanted functionality, and the susceptibility of the product to further deprotonation and oxidation. The reaction tolerates methoxy, acetamido, and nitro substituents on the aromatic ring, as shown in Scheme 24.[31]

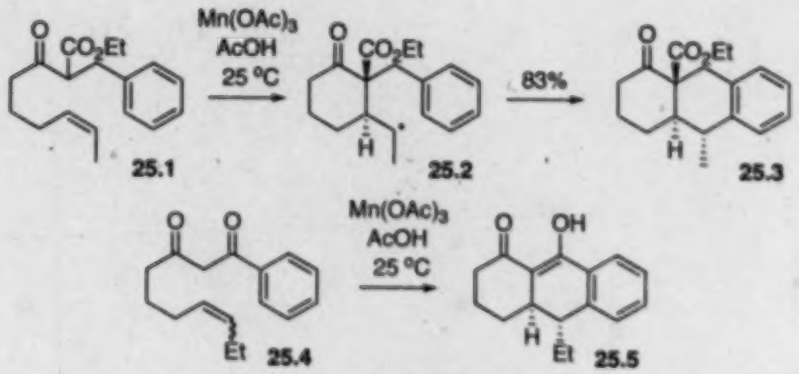


24.1 X = H, OMe, NO_2, NHCOMe **24.2**

Scheme 24

More complex targets can be made by tandem oxidative cyclizations. Oxidative cyclization of **25.1** with $Mn(OAc)_3$ in acetic acid generates a cyclohexanemethyl radical **25.2**. This adds to the aromatic ring to provide **25.3** as a single stereoisomer in 83% yield

(Scheme 25). Similarly, oxidative cyclization of either the *E*- or *Z*-isomer of **25.4** gives **25.5** in 85% yield.[32]



Scheme 25

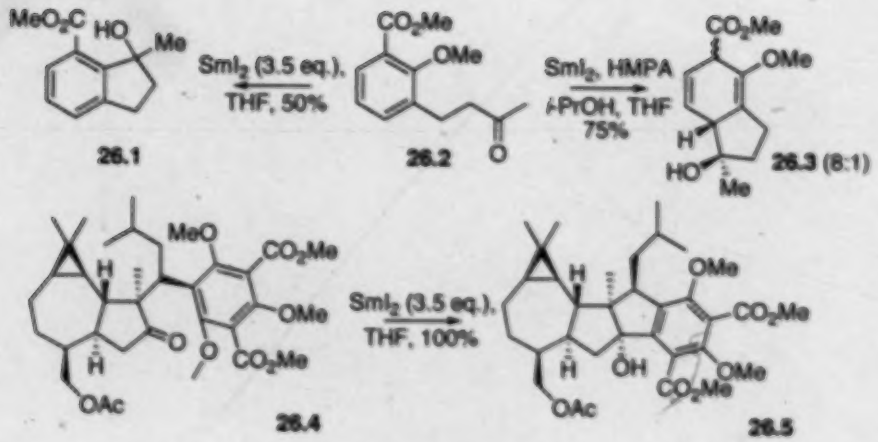
1.1.6 Samarium(II) Initiated Cyclization onto an Aromatic Ring

Samarium(II) diiodide can effect intramolecular radical cyclization onto an aromatic ring if the ring bears an electron-withdrawing group. A few examples of this process are known.[33]

A ketyl radical can selectively attack *ortho* or *para* to an electron-withdrawing moiety, depending on the precise conditions used.[34] Treatment of **26.2** with SmI_2 in THF provides the *ipso*-substituted product **26.1** (50%) through attack *ortho* to the ester. This *ipso*-substitution has been applied to much more complex examples (*cf.* **26.4** → **26.5**). The successful outcome is due to the chelating ability of the samarium ion. The samarium holds the reactants in close proximity, and presumably facilitates the loss of methanol.[34]

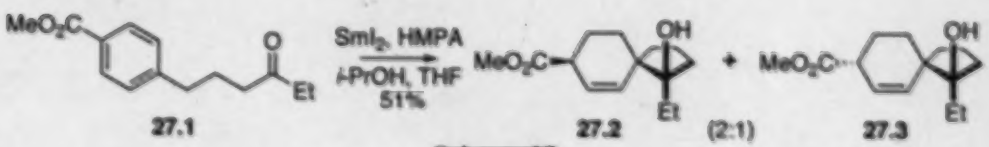
Treatment of **26.2** with SmI_2 (5 equiv.), HMPA (18 equiv.) and *i*-PrOH (2 equiv.) generated the cyclohexadienyl product **26.3** in 75% yield through attack *para* to the ester group.

The same procedure, favoring attack *para* to the electron-withdrawing group, has been applied to the synthesis of spirocycles. It is possible that addition of HMPA and



Scheme 26

isopropanol inhibits interaction of the methoxy lone pairs with samarium; such an interaction would favor a non-chelation controlled pathway. A typical example is shown in Scheme 27. Ketone **27.1** undergoes cyclization using the conditions shown. The radical product of cyclization is reduced by excess SmI_2 to give a 2:1 mixture of diastereomeric alcohols **27.2** and **27.3**.[33]



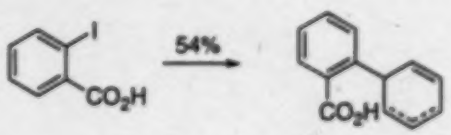
Scheme 27

1.1.7 Radical Cyclization onto an Aromatic Ring without Rearomatization of the Ring

Crich *et al.* have developed conditions where the intermediate cyclohexadienyl radical is trapped without aromatization (*cf.* Scheme 1).[3] The method uses catalytic PhSeSePh which, under radical conditions, generates PhSeH. The selenol facilitates hydrogen atom donation to the intermediate cyclohexadienyl radical. The process is reductive overall and leads to cyclohexadienes.

Intermolecular examples involve slow addition of a solution of Bu_3SnH and AIBN

to an aryl iodide and 20 mol% PhSeSePh in PhH over 12 h (Scheme 28). The highest yielding example involves **28.1** and provided *o*-(cyclohexadienyl)benzoic acid **28.2** in 54% yield (10:1 in favor of the non-conjugated diene). The ratio of non-conjugated to conjugated dienes is due to kinetic trapping of the cyclohexadienyl radical at the internal site. The process is limited to benzene as the radical acceptor and an iodoarene as the radical source. The intramolecular version is very low yielding and leads to mixtures of products.

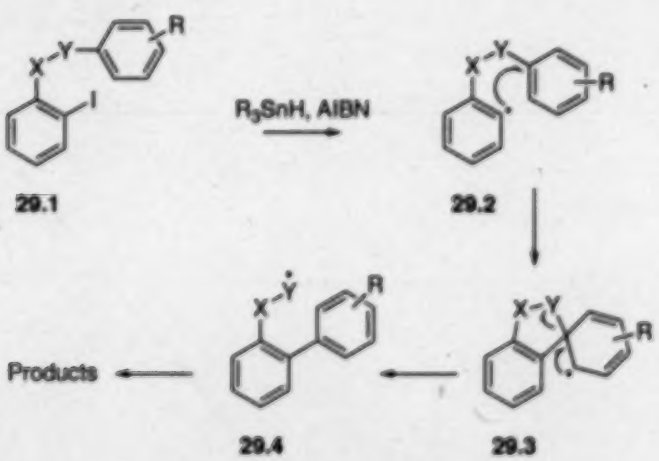


28.1 **28.2**

Scheme 28

1.1.8 Radical Attack on a Benzene Ring, followed by Ipso-Substitution

Intramolecular transfer of aryl groups by a radical mechanism has been known for a long time. The transfer of aryl groups involves *ipso* attack of a radical onto an aromatic

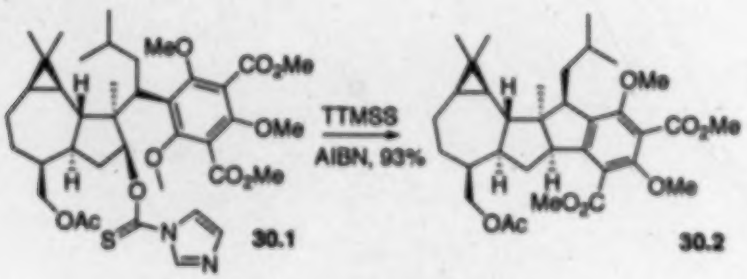


29.1 **29.2** **29.3** **29.4**

Scheme 29

ring. Most of the work involves tethering the radical centre to an aryl acceptor that possesses a good leaving group. A generic case is shown in Scheme 29.[30] Numerous examples are known.[30]

The process shown in Scheme 30 does not appear to be general, but a few closely related, though simpler, examples also work. The outcome is highly dependent on the steric nature of the starting thiocarbamates and the conformation of the radical intermediate. A more successful approach to this *ipso* process involves closing the distance between the radical and the methoxy group, which the strong chelating ability of samarium accomplishes (see Section 1.1.6).[34]

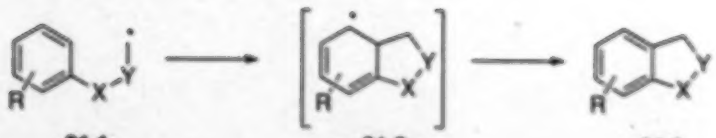


Scheme 30

2 RESULTS AND DISCUSSION

2.1 Research Objectives

The oxidative cyclization of an alkyl radical onto a benzene ring, as shown in Scheme 31 (X,Y = linking chain), would offer a useful route to benzo-fused compounds. As discussed in the introduction to this chapter, this is a known process. However, the only method that appears general is Zard's xanthate method, and this process, brilliant though it is, does suffer from a number of limitations: the use of stoichiometric peroxide and high reaction temperature, the fact that the benzene ring may only be *para*-substituted, and that rings containing a simple carbon chain (*cf.* Schemes 19 and 20) or an oxygen atom (Scheme 22) cannot be formed.



31.1 31.2 31.3

Scheme 31

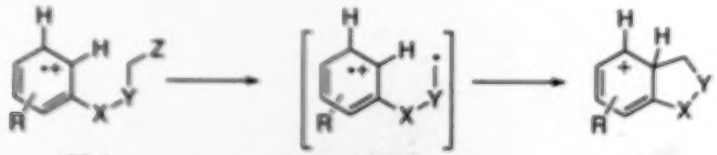
Oxidative radical cyclization is impeded by the energy required to disturb the aromaticity (**31.1** → **31.2**), and the numerous reaction pathways open to the resulting cyclized radical (**31.2**). The addition of peroxide at 160 °C is known to facilitate this oxidative pathway when a tertiary radical adds to an aromatic ring. In some cases polyaromatic species can be formed in good yield by using stoichiometric radical initiator. There is a need for a mild and general procedure that operates under standard radical cyclization conditions.

2.1.1 Development of a Generalized Approach to Radical Cyclization onto a Benzene Ring – An Indirect Method

Our objective was to develop a general approach to oxidative radical cyclization onto a benzene ring. Ideally, the process would allow any carbon radical to cyclize onto any aromatic ring. The chief requirement was that the method should operate under normal radical cyclization conditions.

Oxidative radical cyclization is a multi-step process. The first step, in all published examples, is cyclization onto the ring (Scheme 31, **31.1** → **31.2**), followed by oxidation and elimination of a proton (**31.2** → **31.3**). We realized that if these processes were in a different order then some of the difficulties in the sequence **31.1** → **31.2** → **31.3** might be overcome. A general formula where these processes are indeed in a different order is shown in Scheme 32. If a benzene ring could be oxidized to form **32.1**, and radical cyclization (**32.2** → **32.3**) occurred, then **32.3** would readily lose a proton to regenerate the aromatic ring. There are a number of practical difficulties with this sequence, but a useful

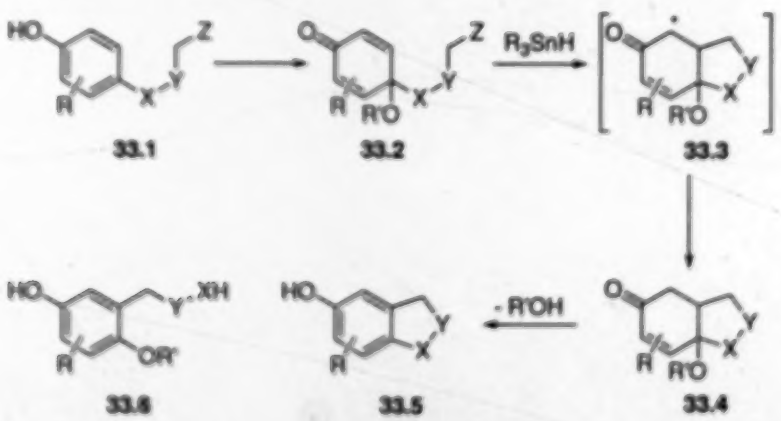
approach may involve temporary modification of the benzene ring in such a way that the system undergoes radical cyclization.



32.1 32.2 32.3

Scheme 32

We decided to explore a plan that relies on a two-electron oxidation of a phenol.[37] Oxidations such as **33.1** → **33.2** (Scheme 33) are well known when X is oxygen. Such an oxidation dearomatizes the benzene ring, and generates a dienone. The ketone functionality in **33.2** activates the olefin for reaction with the incoming nucleophilic radical (**33.2** → **33.3**). The immediate product of radial cyclization (**33.3**) was anticipated to abstract a hydrogen atom from a stannane, and propagate the radical chain. The unsaturated system in **33.3** is unlikely to stabilize the radical intermediate sufficiently to unduly retard the process **33.3** → **33.4** since it is known that α-keto radicals undergo radical chain processes.[38] Homolysis of the C-Z bond in **33.2** may, however, be complicated by the known stannane



33.1 33.2 33.3 33.4 33.5 33.6

Scheme 33

mediated reduction of dienones. Intermediate **33.4** is in the proper oxidation state for acid or base catalyzed aromatization to phenol **33.5**. The conversion **33.4** → **33.5** had another possible complication, in that expulsion of substituent X in **33.4** might occur preferentially, and **33.6** would form instead of **33.5**.

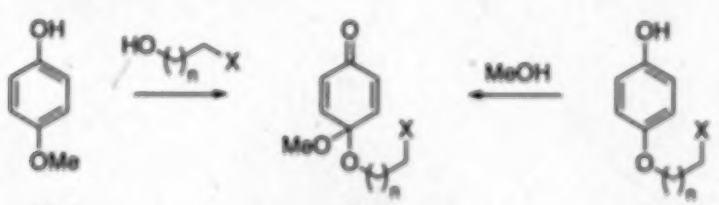
As the oxidation **33.1** → **33.2** is a well-developed process when X is oxygen, we decided to test this sequence on *p*-alkoxyphenols. The use of *p*-alkoxyphenols would ultimately lead to benzo-fused oxygen-containing heterocycles (**33.5**, X = O).

2.2 Formation of Benzo-fused Oxygen Heterocycles

The above indirect method did allow formal radical cyclization onto a benzene ring. The methodology[76] represents a powerful method for making benzo-fused oxygen heterocycles, and standard radical cyclization conditions are used. The individual steps of the method are discussed in the following sections.

2.2.1 Oxidation of p-Alkoxyphenols to Cross-Conjugated Ketones

Cross-conjugated enones **33.2** that carry two alkoxy groups (Scheme 33) are readily prepared by reaction of *p*-methoxyphenols **34.1** in the presence of an α,ω-halo alcohol (see Scheme 34, **34.1** → **34.2**). The best results were obtained when the alcohol was used as the solvent. This process is highly convergent but using a halo alcohol solvent can lead both to solubility problems and difficulty separating the excess alcohol from the product.

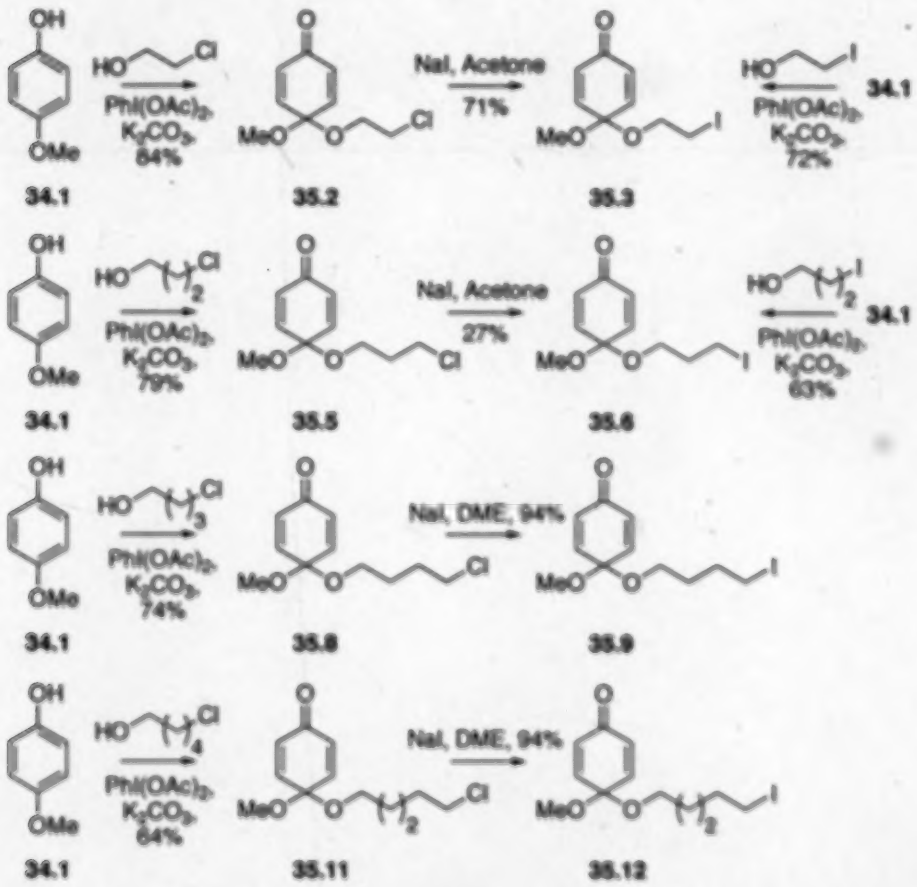


34.1 **34.2** **34.3**

Scheme 34

Alternatively, the starting phenol can carry a *p*-alkoxy group already bearing a halogen (**34.3**), and in that case the oxidation is done in MeOH (**34.3** → **34.2**, Scheme 34).

Typical examples of these approaches are shown in Scheme 35 (for transformations of the type **34.1** → **34.2**) and Scheme 36 (for transformations of the type **34.3** → **34.2**). We generally used $PhI(OAc)_2$ (*ca* 1.1 equiv.) as the oxidizing agent.[40] The intermediate quinone ketals **34.2** are sensitive to acid, and so the oxidation is done in the presence of K_2CO_3 (*ca* 2.2 equiv.) and, during the chromatographic purification, a small amount of Et_3N should be added to all solvents used.



Scheme 35

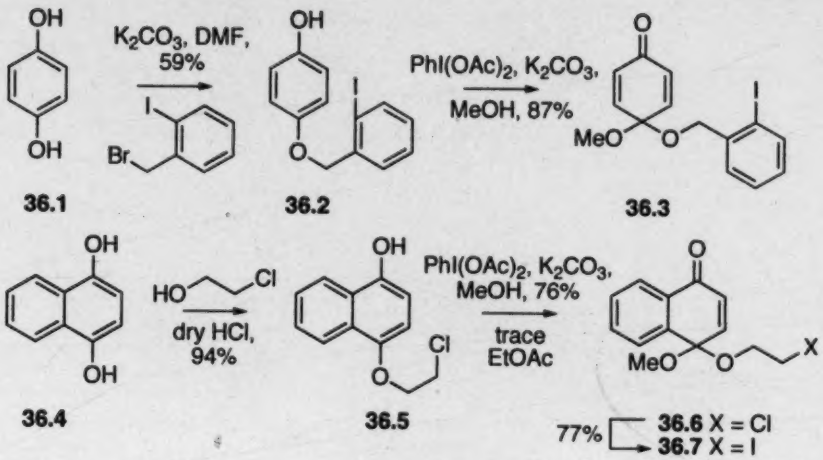
While exploring oxidation conditions it was observed that certain organic solvents and bases (THF, Et_2O, Et_3N, pyridine) are incompatible with $PhI(OAc)_2$, and in these cases poor yields were obtained. Bright blue or bright green colors were also observed in these experiments.

The oxidation process can be done with *some* iodo alcohols (**34.1** → **35.3**, **34.1** → **35.6**), but 4-iodobutanol could not be used as it reacts with $PhI(OAc)_2$. We assume this unwanted side reaction is due, in part, to the ready formation of five-membered rings. The iodide is likely more electron-rich in the case of 4-iodobutanol than when a shorter carbon chain is involved, because the electron-withdrawing oxygen is further removed from the halogen. If the iodide is relatively electron-rich it may interact with the oxidizing agent, become a better leaving group, and so lead to decomposition.

Generally chloro alcohols are satisfactory, and the resulting chlorides can be converted into the corresponding iodides by heating with anhydrous NaI; yields were better when this step was done in dimethoxyethane than in acetone. The yield for the transformation **35.5** → **35.6** was not optimized because a more direct route (**34.1** → **35.6**) was found. Removal of excess halo alcohols, necessary in the general process **34.1** → **34.2** (Scheme 34) can be difficult. In the preparation of **35.8** (Scheme 35), evaporation of excess 4-chlrobutanol (which decomposes to produce THF and HCl) was done in the presence of solid K_2CO_3; the 4-chlorobutanol must also be distilled just before use in the oxidation.

In those cases where a phenol bearing an ω-haloalkoxy group in the *para* position, is readily available (Scheme 36) oxidation in MeOH is experimentally convenient because the excess solvent is easily removed.

Chloride **36.5** was chosen as a starting material simply because its preparation (using dry HCl and 2-chloroethanol) is straightforward.[40] The oxidation of **36.5** to **36.6** is peculiar in that it does not work unless a trace of EtOAc is present; in the absence of EtOAc a complex mixture of products is obtained. Conveniently, a very intense blue color develops



Scheme 36

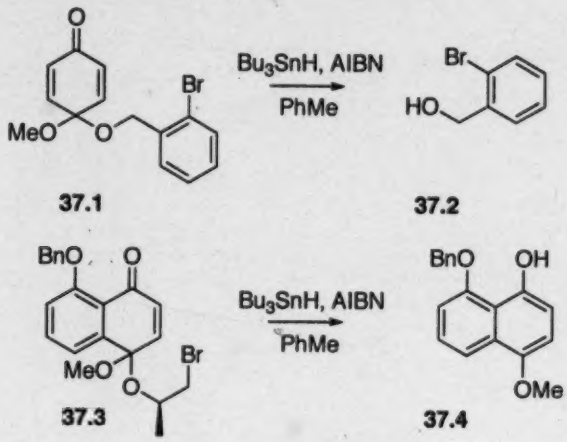
if the reaction does not follow the desired pathway, and so screening of the reaction conditions was greatly facilitated. Freshly chromatographed **36.5** that was dried for a very short time under oil pump vacuum underwent the desired oxidation to **36.6**. Older samples of material that had been transferred to a reaction flask using EtOAc, followed by a short time under vacuum, were also oxidized to **36.6**. The oxidation was repeated several times and was uniformly successful when EtOAc was added, and unsuccessful when it was omitted. We did not attempt to identify the mechanistic basis of this intriguing observation.

2.2.2 Radical Cyclization of Cross-Conjugated Ketones and Rearomatization

The radical cyclizations are discussed below. In each case we used standard conditions, and we arbitrarily avoided refluxing the solvent; we suspect, on the basis of a single experiment, that our milder conditions give a better result. Yields were generally above 75%.

It appears necessary to use iodides in these reactions, as in two examples where bromides were examined (Scheme 37), cyclization did not occur or was a minor pathway:

bromide **37.1** gave alcohol **37.2**, and **37.3** gave **37.4**. Presumably, preferential reduction of the dienone system takes place with these bromides.



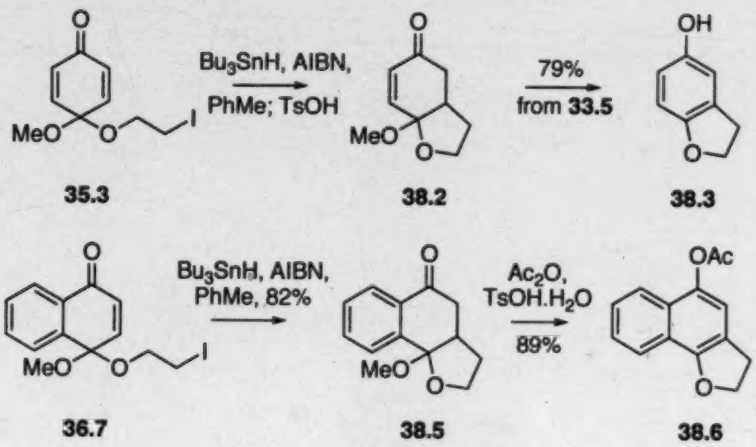
Scheme 37

The formation of dihydrobenzofuran rings (Scheme 38) was readily accomplished by acid-catalyzed aromatization, which is the last step of our overall sequence.

In all of the examples we examined the methoxy group is expelled in preference to the heterocyclic oxygen. $TsOH.H_2O$ is usually satisfactory, but HCO_2H and AcOH can also be used. Slightly acidic $CDCl_3$ and even silica gel were also found to cause aromatization in several cases. Yields for the aromatization are generally above 87%. Conveniently, the crude products from the radical cyclization can be used directly without purification (**35.3** → **38.3**). However, if access to the radical cyclization product is desired it can be readily handled in neutral or basic conditions. The yields of the radical cyclization step are often lowered slightly by partial premature aromatization to the final aromatic product.

The aromatization of **38.5** was initially problematic, and the expected phenol could not be isolated. However, *in situ* acetylation, achieved by acid treatment in the presence of Ac_2O, overcomes the problem and delivers the acetate **38.6** in 89% yield. In this

naphthalene example the phenol generated from aromatization of **38.5**, or by deacylation of **38.6**, is unstable and decomposes rapidly on standing.

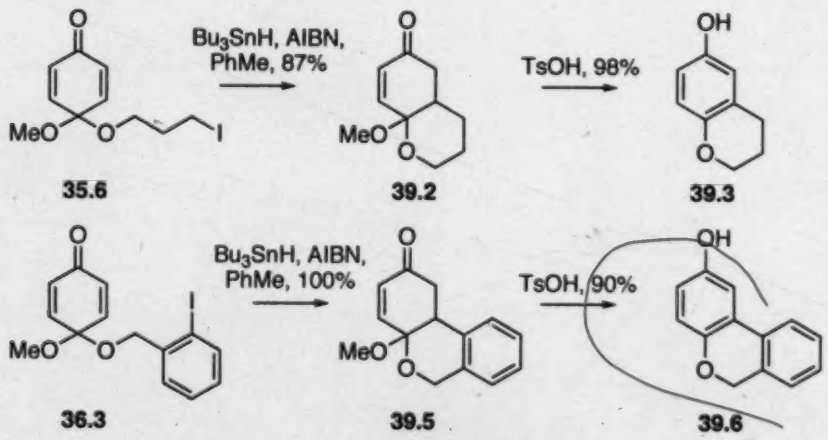


35.3 **38.2** **38.3**

36.7 **38.5** **38.6**

Scheme 38

Formation of six-membered heterocyclic rings by radical cyclization occurred readily. These products (Scheme 39) were smoothly aromatized, using the conditions described above.

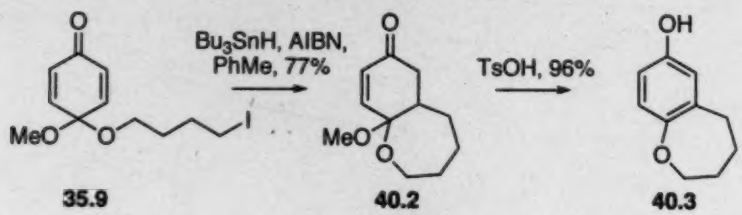


35.6 **39.2** **39.3**

36.3 **39.5** **39.6**

Scheme 39

As seen in Scheme 40, our route also allows the formation of seven-membered rings, normally a difficult process by radical cyclization.



35.9 40.2 40.3

Scheme 40

Of all the iodides examined, only **35.12**, which would have formed an eight-membered ring, failed to undergo radical closure.

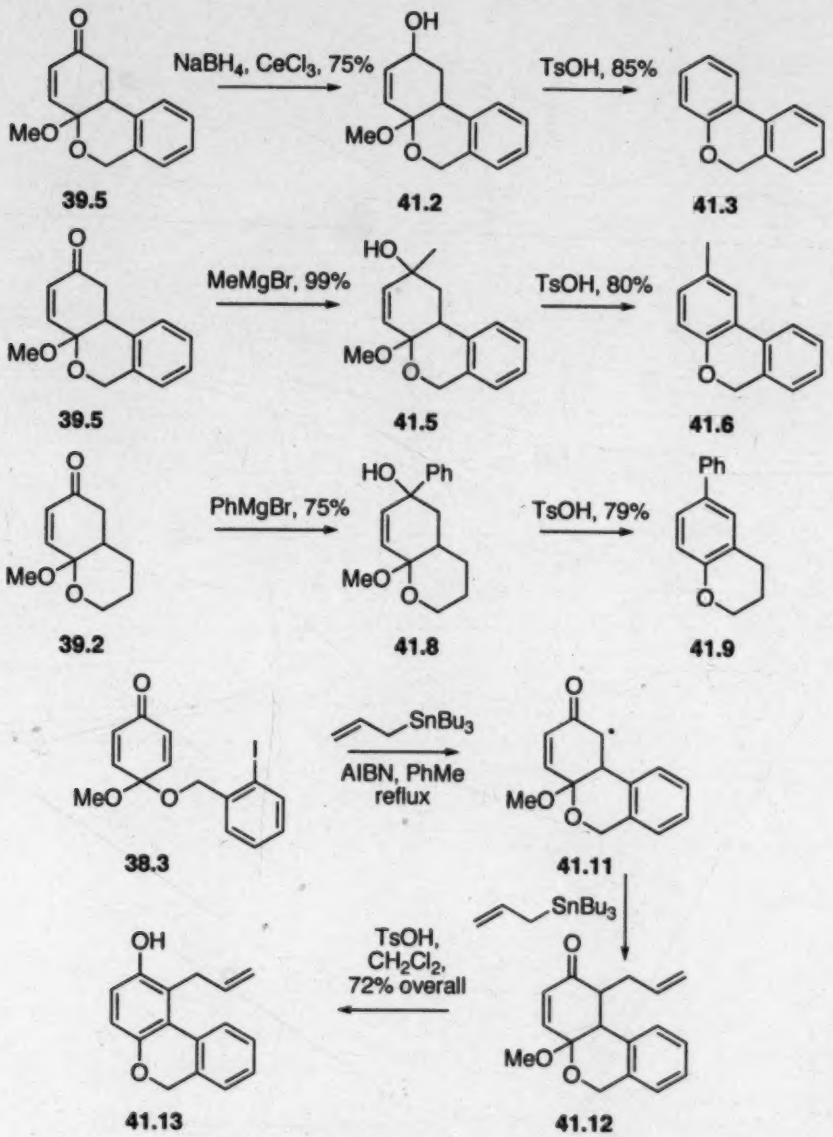
2.2.3 Manipulation of the Radical Cyclization Products before Aromatization

As illustrated above, application of our general process to *p*-alkoxyphenols affords phenols; it can, however, be modified easily so as to produce products with hydrogen, alkyl or aryl groups in place of the normal phenolic hydroxyl.

Reduction of the radical cyclization products with $NaBH_4$ in the presence of $CeCl_3.7H_2O$ proceeds normally (**39.5** → **41.2**), and aromatization of the alcohol that is produced results in loss of the hydroxyl group (**41.2** → **41.3**).

When the radical cyclization products are treated with a Grignard reagent, a tertiary alcohol is formed (**39.5** → **41.5**, **39.2** → **41.8**), and aromatization gives products carrying an alkyl or aryl group originating from the organometallic reagent (**41.5** → **41.6**, **41.8** → **41.9**).

Another modification to the normal sequence that can be made is to trap the intermediate radical arising from the closure step,[42] and this was done in the case of iodide **38.3** (Scheme 41). When the iodide was heated with allyltributyltin and AIBN, radical **41.11** underwent Keck allylation, ultimately giving **41.13**, after acid treatment.



Scheme 41

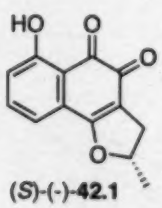
The above results show that the present radical cyclization method is a very effective route to benzo-fused oxygen heterocycles and gives access to substitution patterns not easily accessible by other methods. Additionally, dihydrobenzofuran products are

unavailable by Zard's xanthate route (Scheme 22), and very low yields have been observed when making biaryl oxygen heterocycles by other radical approaches (*cf.* Scheme 10).

Our method was next applied to the synthesis of a sensitive natural product, as described in section **2.3**.

2.3 Application to Natural Product Synthesis: Synthesis of Nocardione A

During the course of the above work the *o*-quinone (-)-nocardione A (**42.1**) came to our attention.[43] The prior synthesis[44] of optically pure material revealed that the structure presents a number of difficult synthetic problems, but it seemed that the compound should be accessible by our radical procedure. The synthesis of nocardione A would be a more demanding test of our method than the examples we had examined so far. Moreover, the nocardiones represent worthwhile synthetic targets on account of their potentially important biological properties.



(*S*)-(-)-**42.1**

Scheme 42

2.3.1 Cdc25 Phosphatases

Protein tyrosine phosphatases are key enzymes in the signal transduction pathway of a wide range of cellular processes.[45] Cdc25 phosphatases control cell cycle progression and regulation. In human cells, three cdc25 genes are present: cdc25A, B, and C, each of which functions at a specific phase of cell division.[46] These phosphatases act by removal of inhibitory phosphates from tyrosine and threonine residues, activating cyclin-dependent kinases.[45]

Cdc25B is expressed throughout the cell cycle, with peak expression in the G_1–S-phase. Cdc25B has oncogenic properties, and is over-expressed in a large number of human cancers including lung, colorectal, gastric, prostate, ovarian cancers, non-Hodgkin's lymphoma and some melanomas.[47] Extensive analysis has shown that 50% of cancers of the head and neck,[48] and 32% of breast cancers are associated with elevated expression of cdc25B.[49] The significant over-expression in a large fraction of tumors suggests that deregulated expression of cdc25 phosphatases may play an important role in cancer development.[48]

The over-expression of cdc25B is also associated with poor survival rates. Out of 124 breast cancer patients studied, those with high levels of cdc25B expression in tumor cells had a ten-year recurrence rate of 42%, while those with little or no expression had a 29% recurrence rate.[49] The percentage of over-expressing patients that died from breast cancer was 37%, while only 20% of cdc25B-negative patients died after 10 years. Of 181 patients with colorectal cancer, high expression of cdc25B was observed in 43% of the cases. The five-year survival rate for those with low expression was 82%, versus 59% for those who over-expressed the phosphatase. The level of cdc25B expression was also found to clearly predict the outcome of patients at different stages of cancer.[50] In addition, cancer proliferation may be promoted by alterations in the function of cdc25b by over-expression.[50] The induction of cdc25B expression in cancer cells may also encourage further development of the cancer, as some known carcinogens have been found to significantly increase the expression of cdc25B in tumor cells, but not in normal cells.[51]

It has been found that the mechanism of action of some benzoquinoid antitumor compounds may involve cdc25B inactivation.[52] Drugs with this mode of action could help improve cancer treatment in various tumors that over-express cdc25B. Head and neck tumors are typically unresponsive to chemotherapy, and despite different protocols that have been explored, aggressive surgery and radiation therapy is the treatment of choice for this tumor type.[49]

As most antitumor drugs show cell cycle-inhibition activity, and are of natural origin, natural product-based inhibitors of cdc25B merit study as leads in drug design. These molecules may also serve as tools to help elucidate the role of important biological pathways and the development of certain cancers.

2.3.2 Isolation and Biological Activity of Nocardione A

Two inhibitors of cdc25B (the nocardiones) were isolated in a program to develop new antitumor agents by finding and exploring inhibitors of specific targets in the cell control cycle. Nocardione A and nocardione B are produced by a microorganism tentatively identified as the Gram-positive bacterium *Nocardia* sp TP-A0248.[40] Only 8 mg of nocardione A and 0.3 mg of nocardione B were obtained from 4.5 L of culture broth. Because of the scarcity of materials the absolute configuration remained unknown until Tanada and Mori's synthesis of (*S*)-(-)-nocardione A and (*R*)-(+)-nocardione B.

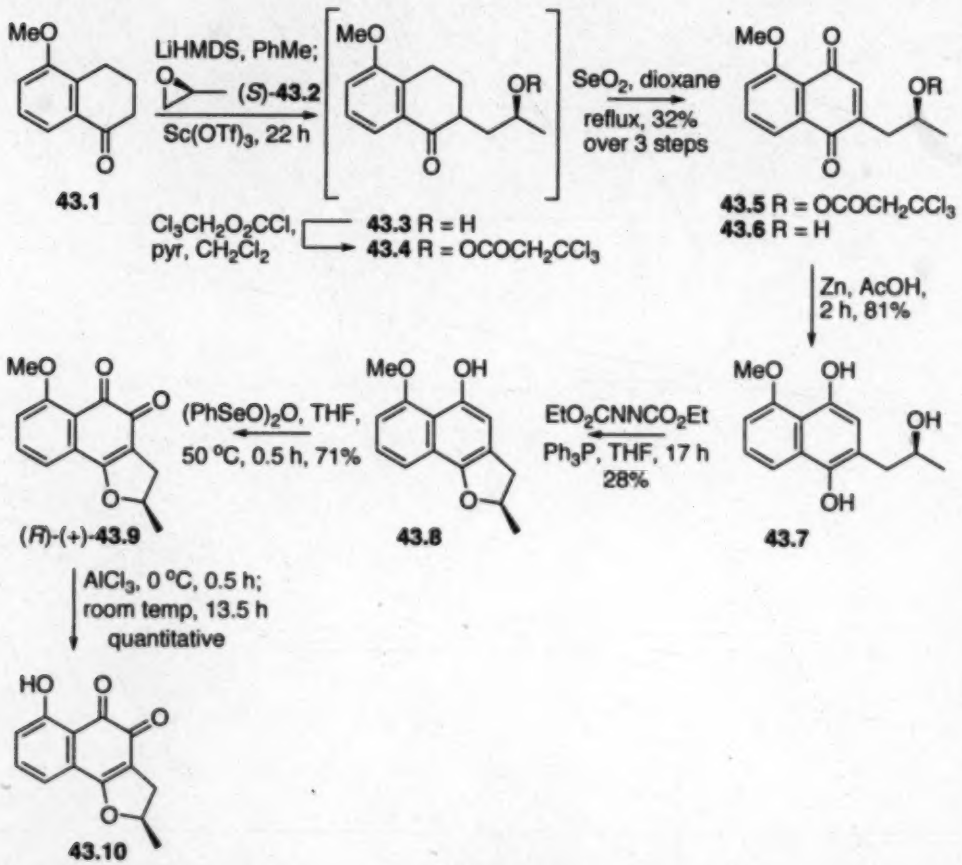
Nocardione A is more active than nocardione B and inhibited the activity of cdc25B phosphatase at a concentration of 10 μM. Nocardione A also has moderate antifungal and cytotoxic activity, and causes cell death with characteristics of apoptosis in U937 human myeloid leukemia cell lines.

2.3.3 Previous Synthetic Work on the Nocardiones

Mori and Tanada's synthesis of nocardione B (Scheme 43), starts with commercially available 5-methoxy-1-tetralone (**43.1**). Treatment with LHMDS, followed by (*S*)-propylene oxide (**43.2**), in the presence of 10 mol% $Sc(OTf)_3$ formed hydroxy ketone **43.3**. Protection of the alcohol was followed by oxidation with SeO_2, to provide **43.5** in three steps (32% yield). Reduction of the quinone with Zn also removed the Troc group, giving **43.7**. The dihydrofuran ring of **43.8** was then constructed through an intramolecular Mitsunobu reaction performed on **43.7**, but the yield under optimized conditions was only 28%.

The dihydrofuran moiety proved to be quite sensitive and attempted oxidation to **43.9** (nocardione B), using various conditions, resulted in ring opening and formation of naphthoquinone **43.6**. Barton's $[PhSe(O)]_2O$ did, however, oxidize **43.8** to (+)-nocardione B (**43.9**) in 71% yield. Demethylation of (+)-nocardione B, to *racemic* nocardione A (±)-**43.10**, proceeded in quantitative yield when using $AlCl_3$, but the procedure caused complete racemization. Other demethylation methods also caused racemization. The overall yield for the six-step synthesis of (*R*)-nocardione B (**43.9**) was 5.1%, based on (*S*)-propylene oxide.

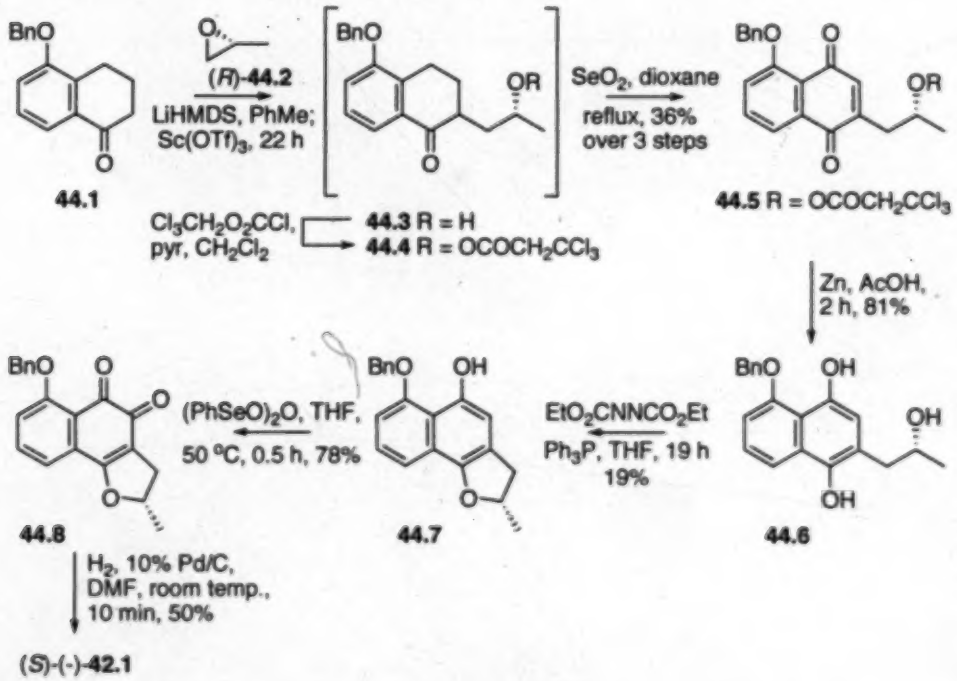
Synthetic (*R*)-nocardione B had a specific rotation of +72.6 ($CHCl_3$), and a melting point of 156-157 °C; it was found to be enantiomerically pure by HPLC analysis on a chiral



Scheme 43

non-racemic stationary phase. The mp and rotation values are different than those reported for the natural (-)-nocardione B [mp 79-81 °C; specific rotation = -29.8 ($CHCl_3$)]; however, the natural product was apparently contaminated, and the impurities were observable by additional signals in the NMR spectra. As the naturally occurring nocardione B is levorotatory, its absolute configuration was determined to be *S*, although there is a slight possibility that impurities in natural nocardione B, might have reversed the sign of its optical rotation.

Mori and Tanada's synthesis of nocardione A (**42.1**) used a similar approach to that shown above, but the phenolic methyl group was replaced by the more labile benzyl group. The sequence starts with the known ketone **44.1** (Scheme 44). The yields of the procedures in the present case are similar to those shown in Scheme 43. Once again, the key



Scheme 44

Mitsunobu reaction proceeded in rather poor yield (19%).

In the benzyl series, deprotection again proved difficult. When 40-50 wt% of Pd on charcoal was used in DMF and the reaction mixture stirred under H_2 for 5-10 min, a 50% yield of nocardione A (**42.1**) was achievable, after the reaction mixture was exposed to air for *ca* 15 min.

The overall yield of Tanada and Mori's synthesis of (*S*)-(-)-**42.1** was 2.2% based on (*R*)-**44.2** (7 steps).

(*S*)-nocardione A was obtained as dark red needles, which melted at 172.5-173.5 °C, and had a specific rotation of -56.0 ($CHCl_3$). These values were again different from those reported for natural (-)-nocardione A [mp 115-120 °C; specific rotation = -85.4 ($CHCl_3$)], but impurities were again apparent in the natural material. The naturally occurring (-)-**42.1** was determined to have the *S* absolute configuration. HPLC analysis of synthetic (*S*)-(-)-**42.1** and comparison with the racemic material produced earlier proved that the present sample was enantiomerically pure.

2.3.4 Total Synthesis of Nocardione A

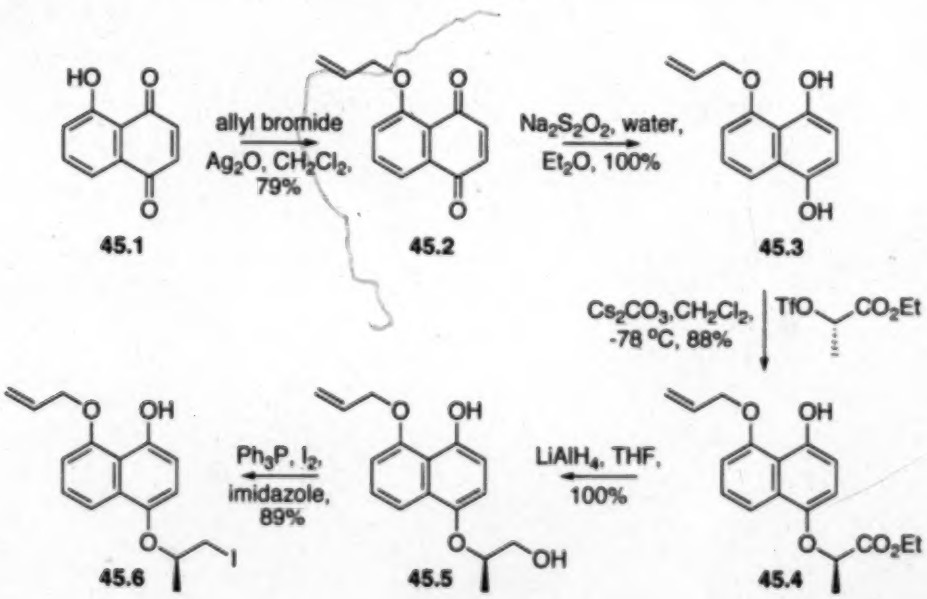
The synthesis of optically pure nocardione A (**42.1**) by Tanada and Mori revealed that the rather innocent-looking structure presents a number of difficult synthetic problems. Their initial route relied on deprotection of the congener *ent*-nocardione B (**43.9**), but attempts to effect the required demethylation caused epimerization at C-2. The successful route was based on *O*-benzyl protection and used a Mitsunobu displacement to generate the delicate dihydrofuran unit (19%). Surprisingly, debenzylation to release the phenolic hydroxyl proved difficult (50%). These problems left the short synthetic route (7 steps from known starting materials) with an overall yield of only 2.2%.

Our approach was to use formal radical cyclization onto a benzene ring to construct the delicate dihydrofuran ring. After the key ring formation, we would follow Tanada and Mori's plan but also explore the use of different protecting groups for the phenolic

hydroxyl. In the event, we prepared *ent*-nocardione A (**47.6**) in 22% overall yield from juglone.

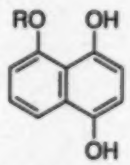
After extensive exploratory work, we settled on the route summarized in Schemes 45 and 47. This route leads to *ent*-nocardione A. Our decision to make the enantiomer of the natural product was based on the relative expense of the optically pure starting material; ethyl (-)-lactate is about 1000 times less expensive than its enantiomer. While a number of procedures are available to synthesize ethyl (+)-lactate there is a lack of reliable and convenient analytical methods to measure the enantiomeric excess of ethyl lactate. It is believed that commercial samples of ethyl (-)-lactate are about 97% ee.[53]

Our synthesis begins with the commercially available natural product juglone (**45.1**), which was protected as an allyl ether (Ag_2O, allyl bromide, 79%) and then reduced to the hydroquinone oxidation level ($Na_2S_2O_4$) (**45.1** → **45.2** → **45.3**). The hydroquinone could be alkylated (**45.3** → **45.4**) with the trifluoromethanesulfonate prepared[54] from (-)-ethyl lactate.



Scheme 45

This step required some optimization and, although a systematic survey of reaction conditions was not made, we did investigate a number of solvents (acetone, DMF, DMSO, CH_2Cl_2), bases (K_2CO_3, Cs_2CO_3), and ethyl lactate derivatives (mesylate and trifluoromethanesulfonate), using the *O*-benzyl (**46.1**), *O*-methoxymethyl (**46.2**), and allyl (**45.3**) hydroquinones.



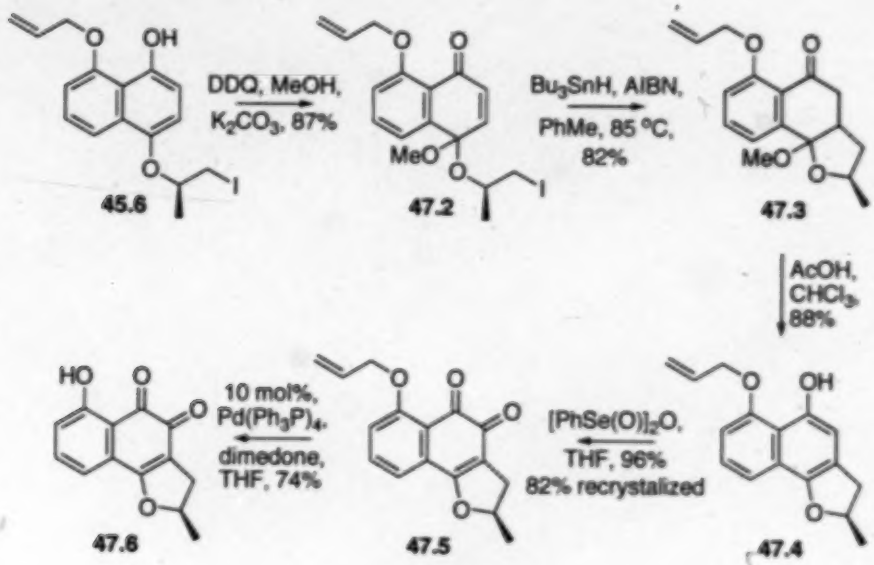
46.1 R = Bn
46.2 R = $MeOCH_2$

Scheme 46

We also examined a Mitsunobu reaction between **46.1** and ethyl lactate, but the yield of the coupled product was poor and extensive amounts of quinone were generated. It is possible that the poor yield of the Mitsunobu reaction to form the dihydrofuran ring, reported by Tanada and Mori (*cf.* **43.7** → **43.8**, Scheme 43), may be due to hydroquinone oxidation under Mitsunobu conditions. The authors reported that **43.7** is quite sensitive to oxidation by air, and it may be sensitive to oxidation in general.

These experiments guided us to the conditions summarized in Scheme 45, and we accepted the modest yield (50%) for the alkylation (**45.3** → **45.4**) since much hydroquinone could be recovered, so that the corrected yield was 88%. In addition, alkylation occurred only at the required phenolic hydroxyl under the optimized conditions. This process, unlike the others we explored, worked with clean inversion of the lactate stereochemistry (as judged by ^{19}F NMR examination of the Mosher ester derived from alcohol **45.5**). This stereochemical outcome requires that ethyl (+)-*R*-lactate be used to make natural nocardione A.

Ester **45.4** was then reduced (Scheme 45, $LiAlH_4$, 100%, **45.4** → **45.5**); surprisingly, reduction of the corresponding ester in the methoxymethyl series (derived from **46.2**) gave erratic results. With alcohol **45.5** in hand, iodide **45.6** was easily obtained by reaction with Ph_3P, I_2 and imidazole (89%).

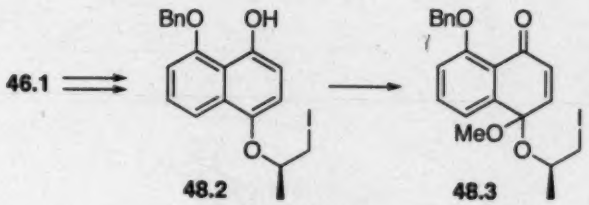


Scheme 47

At this point, oxidation of **45.6** with DDQ in MeOH afforded the substrates **47.2** (Scheme 47) required for the key radical cyclization (87%). The choice of DDQ, as opposed to $PhI(OAc)_2$, was based on earlier studies in the benzyl series, where the corresponding transformation (Scheme 48, **48.2** → **48.3**) was very inefficient with $PhI(OAc)_2$, but improved significantly when DDQ was used. Our earlier work on the oxidation of **36.5** → **36.6**, which required a trace amount of ethyl acetate to be successful, had already shown that naphthalene-derived structures can be problematic oxidation substrates.

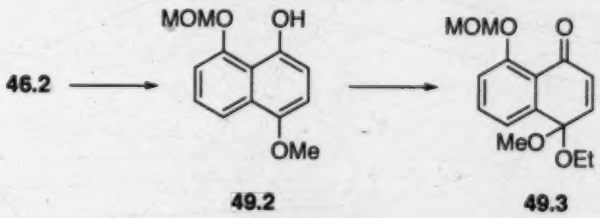
An alternative method for making cross conjugated ketones such as **47.2** was investigated briefly: the hydroquinone *O*-methyl ether **49.2** (Scheme 49) was treated with

DDQ in neat ethyl lactate, but we did not isolate the expected product, and obtained instead the mixed acetal **49.3**.



Scheme 48

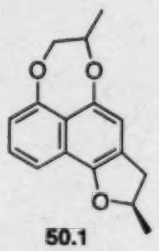
Radical cyclization of **47.2** (Scheme 47) under standard conditions gave the desired product **47.3** in 82% yield; evidently, the intermediate radical is quenched by stannane rather than undergoing closure through oxygen onto the double bond of the allyl group (*cf.* Scheme 50). This result may indicate that the immediate radical products of cyclization are carbon based, and, as shown earlier, Keck reaction conditions (Scheme 41, **38.3** → **41.11** → **41.12**) cause alkylation at carbon. Quantitative aromatization (^{1}H NMR) of **47.3** to **47.4**



Scheme 49

occurred on storing the cyclization product in $CDCl_3$; use of HCO_2H gave some **47.4**, but an appreciable amount of the cyclic ether **50.1** (as a mixture of two isomers) was also formed. Treatment of **47.3** with DBU in refluxing PhMe (12 h) caused no change. The evident stability of these acid-sensitive ketones to basic conditions may prove to be a useful

property in other work. Satisfactory rearomatization (**47.3** → **47.4**) was easily achieved by using AcOH in $CHCl_3$ at room temperature (88%).



50.1

Scheme 50

Naphthol **47.4** was converted (96%) into the *o*-quinone **47.5** by the action of $[PhSe(O)]_2O$ in the same manner as used in Mori's synthesis.[44] The quinone was recrystallized (82% yield after recrystallization) and then treated with $(Ph_3P)_4Pd$ in the presence of dimedone to remove the allyl protecting group and release *ent*-nocardione A (**47.6**, 74%).

We found *ent*-nocardione quite difficult to purify. Effective purification first required the use of an acidified solvent system (0.1:10:90 HCO_2H-EtOAc-$CHCl_3$) during flash chromatography over silica gel. This procedure allowed recovery of much of the product in the form of a crude red powder. Recrystallization (EtOAc-hexane) was then necessary to give pure (*R*)-(+)-nocardione A, in the form of curled red needles: mp 168-169 °C. If the crystalline material is dissolved in a solvent and the solution evaporated to leave a powder, the powder changes to needles (mp 168-169 °C) at or below 158 °C.

The value of the specific rotation of *ent*-nocardione A in $CHCl_3$ was found to vary with the length of the cell used. This effect is due to the deep red color of the product, which does not allow sufficient transmission of light through our instrument. Mori's values for (-)-nocardione A was -56.0 at c = 0.97 in $CHCl_3$, while that reported for natural (-)-nocardione A was -85.4 at c = 1.0 in $CHCl_3$. These absolute values are considerably

higher than what we had observed, but neither of the values reported in the literature mention the cell length used. Our synthetic (+)-nocardione A (in a standard 10-cm cell) had a specific rotation of only +36.8 at c = 1.0 in $CHCl_3$. However in a 1-cm cell the observed value was +49.5 at c = 0.97 in $CHCl_3$, a value which is closer to Mori and Tanada's result. Apparently the natural material contains impurities that are detectable in the ^1H NMR spectra,[44] and this may affect the value of rotation.

The optical rotation data seemed inappropriate for measurement of the enantiomeric excess of our material, and so our sample was analyzed by HPLC with a chiral non-racemic stationary phase. Under the conditions used, (*S*)-(-)-nocardione A was detected at a retention time of 40.31 min, while (*R*)-(+)-nocardione A was detected after 42.82 min. Our synthetic (*R*)-nocardione A was found to have an ee of 98.55%.

As already indicated, in preliminary work along similar lines to those summarized in Schemes 45 and 47, we had used *O*-benzyl protection, but removal of the *O*-benzyl group in the last step of the synthesis could be achieved in only 43% yield. We also explored *O*-MOM protection, but found that reduction of the ester unit (*cf.* **45.4** → **45.5**) then gave variable yields, and at the end of the sequence (*cf.* **47.5** → **47.6**) the MOM group could not be removed without opening the dihydrofuran ring. Therefore, we tried the *O*-allyl group, and found that it was satisfactory, as described above. Its use, in combination with the radical cyclization methodology, allows construction of *ent*-nocardione A in an overall yield of 22% from juglone (**45.1**), ten times the yield observed in Mori's synthesis. Our radical cyclization procedure overcomes the previous limitations in constructing substituted benzo-fused dihydrofuran rings by previously known methods.

2.4 Formation of Benzo-Fused Nitrogen Heterocycles

The process in Sections 2.2 and 2.3 forms benzo-fused oxygen heterocycles and relies on oxidative dearomatization of a *p*-alkoxyphenol as the key step. Application to the

formation of nitrogen-containing heterocycles would provide access to a broad range of structures found in biologically active molecules.

The extension of our method to the formation of dihydrindole and higher homologues appeared especially worthwhile as there does not appear to be a general method for the formation of such heterocycles, and a method that offered stereochemical control of the substituents on the nitrogen-containing ring would be especially useful.

Below is described synthetic work that allows extension of our original general method to saturated nitrogen containing benzo-fused heterocycles.

2.4.1 Synthetic Considerations

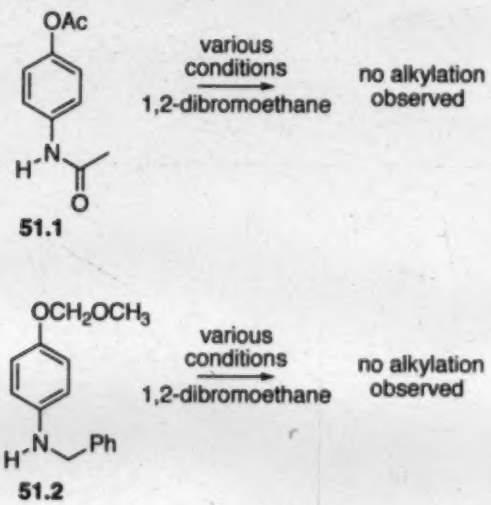
Unlike the above oxidations which involve phenols with oxygen-containing chains (X = O, **33.1** → **33.2**, Scheme 33), the equivalent oxidation when X is a nitrogen unit is not at all well known. The trivalent nature of nitrogen meant that X would represent NR, and various values of R would have to be evaluated. Unlike the case of X = O, this required extensive exploration of the oxidation process itself, and practical synthetic routes to **33.1** (containing a free phenol, X = NR, and Z = I) had to be developed.

2.4.2 Evaluation of Routes to p-Amino Phenols

Initial approaches involved alkylation of a monoprotected amine using an α,ω-dihalo carbon chain. However, attempted alkylation of **51.1** under a range of conditions gave very little product or none at all (Scheme 51).[35] The MOM-protected benzyl amine **51.2** could be alkylated with MeI and K_2CO_3 in DMF, but more complex carbon chains such as dibromoethane and its synthetic equivalents could not be added, even under forcing conditions.

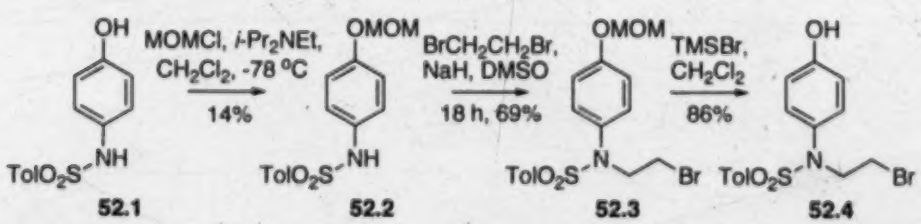
In other exploratory work, alkylation occurred when a tosyl-protected amine was used. Selective protection of the phenol moiety of **52.1** gave **52.2**, in low yield. No attempt was made to improve the yield, but the compound was alkylated directly with 1,2-

dibromoethane (**52.2** → **52.3**). Removal of the MOM group provided the oxidation precursor **52.4**. To our disappointment we were unable to oxidize **52.4**, using standard conditions [$PhI(OAc)_2$, K_2CO_3, MeOH], and the starting material was recovered even after heating. Oxidation with DDQ in MeOH, as used in the nocardione A synthesis, also gave



Scheme 51

no reaction, even at the reflux temperature of MeOH. The use of other oxidizing agents such as CAN, $Pb(OAc)_4$, or $Tl(NO_3)_3$ was also unsuccessful. With CAN an *o*-diphenol was formed, $Pb(OAc)_4$ caused no reaction unless used in excess in AcOH, and then the bromine was replaced by AcO; the thallium reagent gave an unidentified compound

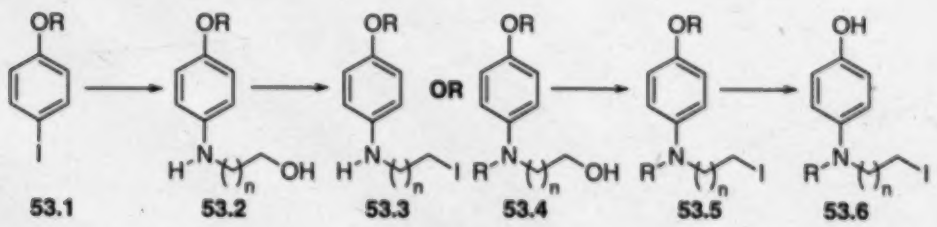


Scheme 52

lacking the alkyl chain. It appeared that the formation of cross-conjugated ketones in the nitrogen series would require protecting groups other than sulfonates.

In the interest of developing a useful general procedure we abandoned approaches relying on the alkylation of a pre-existing amine, and instead we evaluated a number of synthetic routes in order to identify a preparative sequence to *p*-aminophenols **33.1** in which several closely linked requirements were each satisfied in a mutually compatible way.

Eventually, our approach to nitrogen heterocycles became designed around a cross-coupling strategy. This confers several advantages, primarily that the transformation of **53.1** → **53.2** (Scheme 53) is convergent. Consequently, the aryl iodides and/or the amine can be independently modified before coupling. Also, the twenty natural amino acids and their derivatives can be readily transformed into amino alcohols for potential use in the coupling. These readily available enantiomerically pure building blocks should allow access to potentially valuable structures.



Scheme 53

To develop the sequence outlined in Scheme 53, we tried several copper mediated coupling procedures. The method recently developed by Ma,[56] which uses amino acids as ligands, was found to be very convenient. In the event, when we applied Ma's conditions, the coupling of *unprotected* amino alcohols with *O*-protected *p*-iodophenols worked nicely. The experiments described below clearly demonstrate the compatibility of this coupling procedure with unprotected alcohols — a characteristic that is clearly a useful feature. The free alcohol moiety not only serves as a handle for subsequent manipulation, but it appears

to actually improve the cross coupling reaction. The yields of these coupling reactions are easily comparable to the yields reported for unfunctionalized examples from Ma's laboratory. We also found that when amino alcohols were used, the reaction proceeded at lower temperatures and/or required shorter reaction times. This effect is likely due to the lone pairs on the oxygen atom allowing the amino alcohol to act as a bidentate chelate to the metal catalyst, which facilitates coupling after oxidative addition of copper to the C-I bond.

On small reaction scales (*ca* <1 g of aryl iodide) these coupling procedures seem to work best at a concentration of 1 M or less; slower reactions and lower yields were observed at higher dilution. However, when these reactions are done on scales involving >1 g of aryl iodide, higher dilution (*ca* 0.5-0.75 M) appears to be necessary to maintain good yields. In these larger scale reactions done at high concentration the mixtures were usually found to solidify after *ca* 30% conversion.

We also found that after the coupling, formation of the iodide can be carried out before or after protection of the amine nitrogen (*cf.* Scheme 53). This possibility offers some unanticipated flexibility to the sequence. If MOM ethers are used for phenol protection, Me_3SiBr readily removes the protecting group.

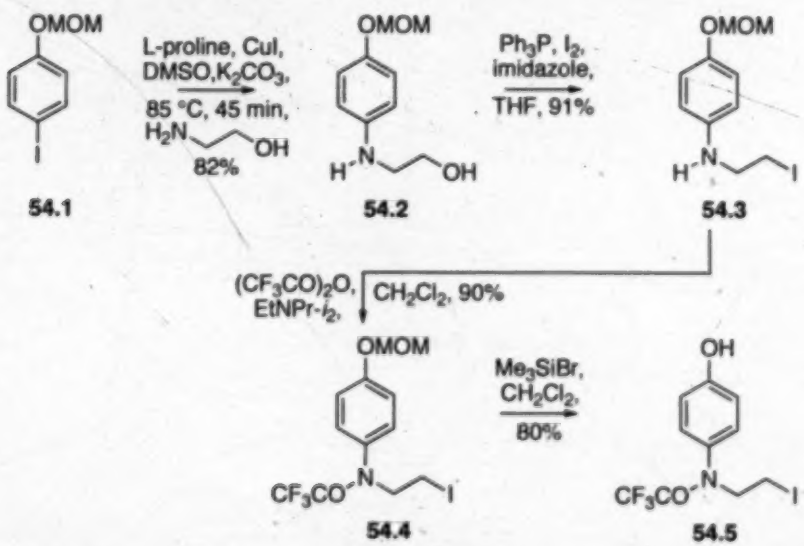
The route outlined in Scheme 53 involves several steps from protected iodophenols to *p*-aminophenols, but we have also developed procedures that do not require phenol protection. In addition we have used secondary amides instead of amines. Such sequences are convenient as they shorten the overall route.

Many of the reactions discussed below rely on the formation of *tertiary* amines. Our experience has shown that the amines **53.4**, and **53.5** and their further elaboration products have complex NMR spectra with very broad signals. Presumably, this is due to restricted rotation about one or more carbon-nitrogen bonds.

2.4.3 The First Generation Approach

(a) Preparation of p-Amino Phenols

The preparation of substrates to examine the oxidation process began by cross coupling 2-aminoethanol with **54.1** using Ma's procedure. This reaction was found to occur rapidly (45 min) at 85 °C to form **54.2** (82%). We were then able to form and isolate iodide **54.3** (91%); but the nitrogen had to be protected promptly, to give **54.4** (90% yield). Amino iodide **54.3** is somewhat unstable and it definitely should be used the same day or stored at -78 °C. An attempt to make the acetate corresponding to **54.4** using acetic anhydride, did not work, and we suspect that the desired acetamide forms and then undergoes further reactions. Deprotection of iodide **54.4** was readily achieved with Me_3SiCl (80%), but treatment with BBr_3 also provided **54.5** (74% yield).

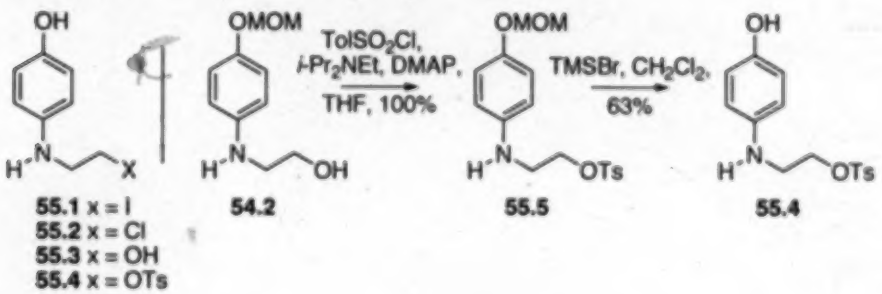


Scheme 54

It appears that protection of the phenolic hydroxyl group of **54.3** is necessary, as the free phenol corresponding to **54.3** could not be isolated. Attempted deprotection of **54.3**

with Me_3SiBr, which would provide **55.1** (Scheme 55) led to immediate decomposition. The chloro analog of **54.3** (which would provide **55.2**) gave the same result upon deprotection with Me_3SiBr. Compound **55.2** also could not be prepared from **55.3**. There may be a delicate electronic balance that affects the stability of secondary amines bearing a 2-halo substituent, and removal of the MOM group tips this balance toward decomposition. Once the amine is blocked the phenol can be deprotected (*cf.* **54.4** → **54.5**).

What we believe is compound **55.4** could be readily prepared by monoprotection of **54.2** with TsCl (*ca* 100%), followed by deprotection (63%). We were not able to exclude the possibility that the tosylation of **54.2** occurs on nitrogen, and so the structures of **55.5** and **55.4**, and therefore **57.2** (see later), are tentative assignments.



Scheme 55

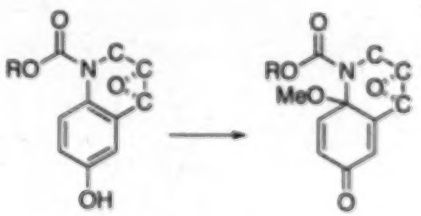
(b) Oxidation of p-Amino Phenols

The key intermediates of our method are cross-conjugated ketones **33.2** (X = NR) and, having found preparative sequences to aminophenols **33.1**, their oxidation was then examined. The oxidation products are themselves potentially useful intermediates, although we did not explore possible applications.

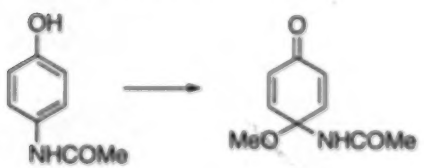
While hundreds of oxidations of the type **33.1** → **33.2** (X = O) have been published, the only relevant examples for aminophenols are found in synthetic work on the dynemicin A chromophore (**56.1** → **56.2**, Scheme 56) by the groups of Danishefsky and

Myers.[57] There is also a report that **56.3** is convertible into **56.4** on treatment with $PhI(OAc)_2$.[58]

Oxidation of **55.4** (structure tentative), using the conditions described in Section 2.2.1 [$PhI(OAc)_2$, K_2CO_3, MeOH], failed. It appears that, at least in this transformation, the presence of K_2CO_3 inhibits the reaction. Smooth oxidation (65%) to **57.2** (structure tentative) was observed when the base was omitted. This result was repeatable, but we did not explore why the oxidation **55.4** → **57.2** (structures tentative) does not occur in the presence of K_2CO_3. We did perform an experiment that involved careful neutralization of the initially present base by the addition of acetic acid and, while there was no initial reaction, oxidation to **57.2** did occur upon neutralization.



56.1 R = allyl, Me **56.2**



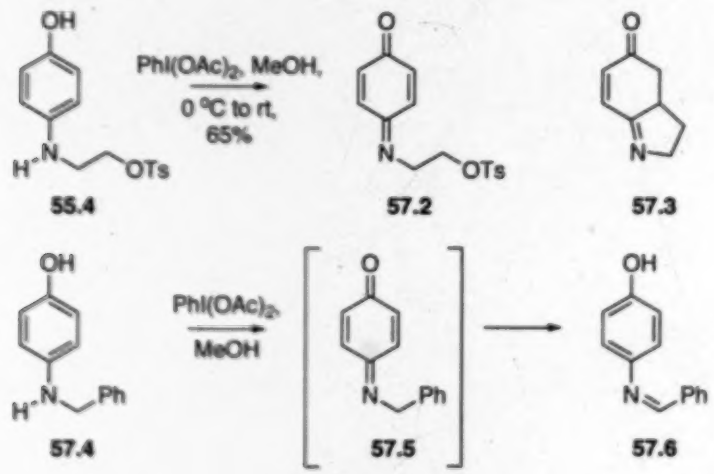
56.3 **56.4**

Scheme 56

Unfortunately radical cyclization of quinone imines related to **57.2** (to allow access to **57.3**) could not be explored, as we were unable to make suitable radical precursors.

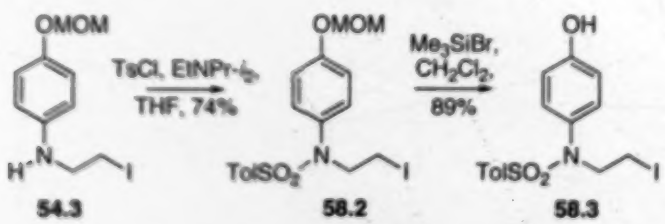
Attempts to replace the tosylate moiety in **57.2** (structure tentative) with iodine (>10 equiv. NaI, hot acetone) provided only recovered **57.2**. Changing the solvent to refluxing glyme (2 days) gave the same result. Conversion to an unidentified product that still

contained the tosyl group was observed when **57.2** was deliberately heated for 2 days at 100 °C with NaI in the absence of solvent. Oxidation of **57.4** to **57.5**, as a model study, was unsuccessful, and **57.6** was obtained. It is possible that the desired product (**57.5**) formed and then gave **57.6** spontaneously.



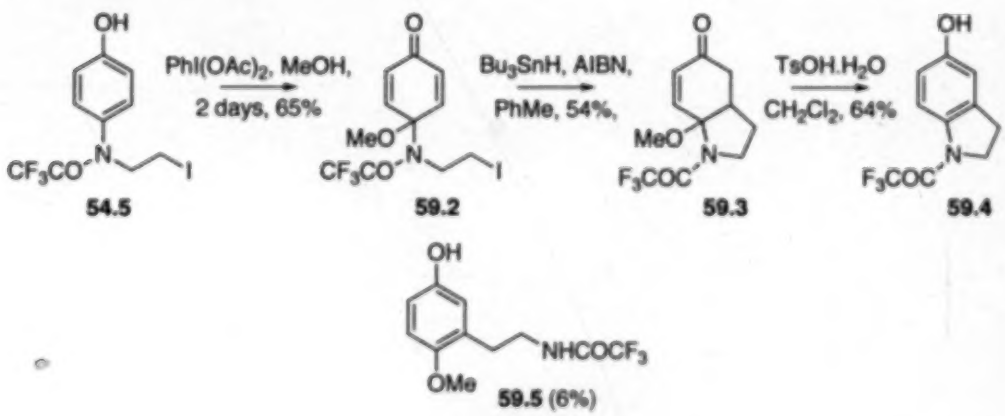
Scheme 57

Although oxidation of the *N*-tosyl bromide **52.4** was unsuccessful, we tried to oxidize the *N*-tosyl iodide **58.3**, which is readily available from **54.3** (Scheme 58). Attempts to use $PhI(OAc)_2$ in the absence of base gave recovered **58.3**. Switching to $PhI(OCOCF_3)_2$, a more powerful oxidizing agent, provided two unidentified products (neither of which contained an MeO group) and recovered starting material.



Scheme 58

We then turned our attention to the *N*-trifluoroacetoxy protected phenol **54.5**. Oxidation, in the absence of base, was found to proceed slowly (2 days) using $PhI(OAc)_2$ in MeOH (Scheme 59), however, the yield was acceptable (65%). Use of $PhI(OCOCF_3)_2$ gave the same product. In this case the reaction was faster (30 min) and appeared to be very clean. TLC monitoring and ^1H NMR analysis of the crude reaction mixture both indicated that **59.2** was the only product; however, the yield of isolated **59.2** was only 53%. A sample of **59.2** that was added to water and then extracted using our workup procedure only gave 82% recovery of the material. Recovery of a sample subjected to flash chromatography was 90%. Based on these observations we suspect that the yield for the transformation **54.5** → **59.2** could be improved by modifying the isolation.



Scheme 59

(c) Radical Cyclization and Aromatization

The radical cyclization **59.2** → **59.3**, using standard conditions, appeared to proceed smoothly. The yield, however, was only 54% after subjecting the material twice to flash chromatography (64% after correction for recovered starting material). The products of reactions mediated by stannanes can be difficult to separate from tin byproducts. It

appeared that the polarity of the product made this separation especially difficult, and we suspect that the low yield is due to losses of **59.3** during chromatographic isolation.

The aromatization step can, in principle, proceed in two ways, depending on whether the methoxy group (**33.4** → **33.5**, Scheme 33) or the amino unit (**33.4** → **33.6**) is expelled; in the case of oxygen heterocycles the desired loss of the methoxy group is the only pathway we observed. Rearomatization of **59.3**, using the conditions of Section 2.2, gave bicycle **59.4** as the major product (64% yield), but this was accompanied by **59.5**, which was obtained in 6% yield. The use of $CDCl_3$ (1 week), and formic acid ($CHCl_3$, 1 week) both gave unchanged **59.3**.

Complete selectivity for the desired **59.4** (as judged by the ^1H NMR spectrum on the crude reaction mixture) was observed when 4Å molecular sieves were used in combination with the action of $TsOH.H_2O$.

The above first generation approach to *N*-heterocycles illustrated that the use of the trifluoroacetoxy group may not be ideal. The oxidation was slow, the yields were moderate, and the products of oxidation and radical cyclization seemed difficult to handle. Consequently, it was decided that different *N*-protecting groups should be explored.

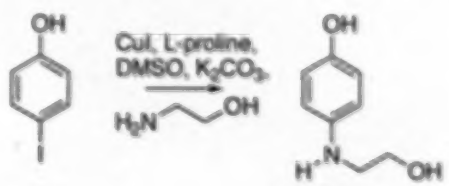
2.4.4 Second Generation Approaches

The successful sequence of oxidation, radical cyclization, and aromatization described above uses $COCF_3$ protection of the amine. Other nitrogen substituents (H, $COCH_3$, SO_2Tol) were unsuccessful. Carbamates were used in the aminophenol oxidations by Danishefsky and Myers and, although we were unaware of that work at the time, we felt that carbamates were worth exploring. Carbamates can also be used to selectively protect an amine in the presence of hydroxyl groups. Such a selective protection would allow our synthetic route to skip formation of unstable iodoamines (*cf.* **54.3**) and proceed through alcohols **53.4** instead. It also seemed worthwhile to attempt Ma's procedure with *unprotected* amino alcohols and *unprotected* iodophenols. If these experiments were

successful, and if *N*-protection could be accomplished in the presence of both unmasked phenols and alcohols, our synthetic route would be shortened.

(a) Cross-Coupling to Form Unprotected Aminoalkoxy-Phenols and Subsequent Manipulation

Initial examination of the reaction **60.1** → **60.2** (Scheme 60) at 85 °C, suggested that the product was formed in good yield (TLC) after 40 min, but the isolated yield was only 3%. More product could be obtained by using a very rigorous extraction procedure that involves neutralizing the quenched reaction mixture to pH 7, saturating this solution with solid NaCl, and then performing multiple extractions with EtOAc. The reaction conditions were then optimized for temperature, using 2 equiv. ethanolamine, and a temperature of 60 °C for 30 h was found to be best, giving a 75% yield of **60.2**.[80] A modification of this procedure using 5 equiv. of the inexpensive amine, and heating for 3 h at 55 °C, provided **60.2** in 81% yield. Exploratory work had illustrated that keeping the reaction temperature below 60 °C suppressed formation of byproducts.



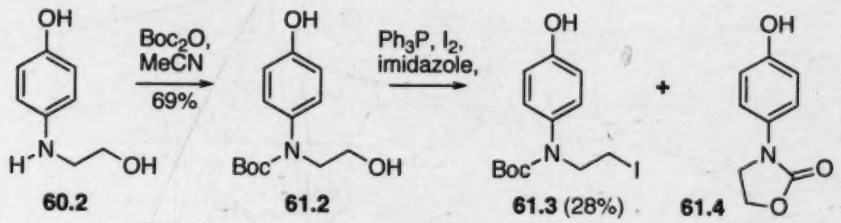
60.1 **60.2**

Scheme 60

The first carbamate we examined was the Boc group. Treatment of **60.2** with Boc_2O in MeCN gave a 69% yield of **61.2**. Formation of the iodide was then achieved in low yield (28%), the major product obtained being the cyclic carbonate **61.4**. Evidently, intramolecular participation of the Boc carbonyl occurs during activation of the alcohol by the Ph_3P, I_2 combination.

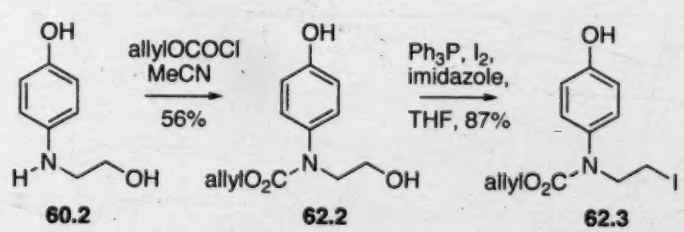
When we attempted to oxidize compound **61.3**, complex mixtures of products (without MeO incorporation) were obtained.

The use of other carbamates was explored in the hope that the Boc group was uniquely incompatible with our synthetic plan, possibly because of the ready formation of a *t*-butyl carbonium ion.



Scheme 61

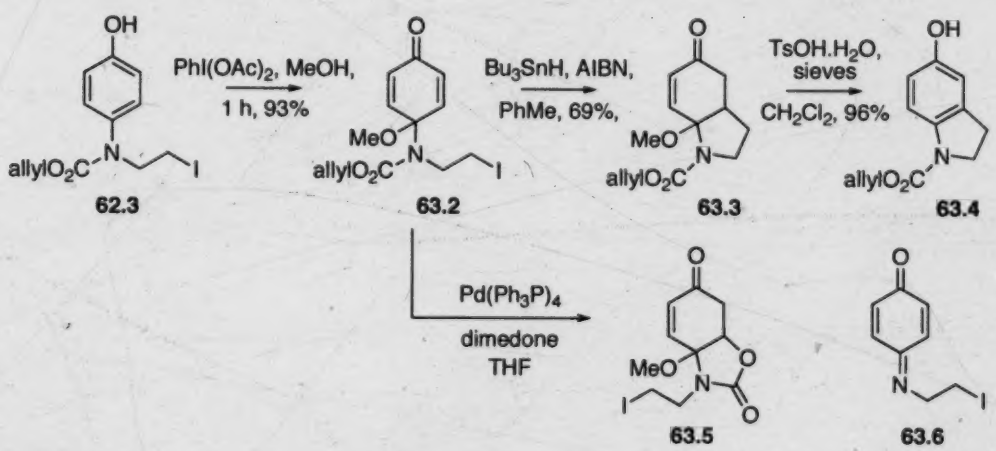
The alloc group proved suitable, but its use was initially problematic. Selective protection of the amine function in **60.2** could not be accomplished if base was added during the transformation **60.2** → **62.2**. Simply injecting allyl chloroformate into a solution of **60.2** in MeCN gave an acceptable yield (56%). A multistage procedure, similar to the method necessary for methyl carbamate protection (**60.2** → **64.2**) (see later), improved the yield only to 62% in the present case. Formation of iodide **62.3** was efficient if an excess (*ca* 2.5 equiv.) of the reagents was used; under these conditions formation of **62.3** was accompanied by only a small amount of **61.4**.



Scheme 62

Oxidation of **62.3** to **63.2** was fast and clean; either PhIO (40 min, 84%) or $PhI(OAc)_2$ (1 h, 93%) could be used as the oxidizing agent. The oxidation product (**63.2**) is readily converted (Scheme 63) into the desired aromatic phenol (**63.4**). Radical cyclization (**63.2** → **63.3**, 69%) and rearomatization (**63.3** → **63.4**, 96%) were efficient.

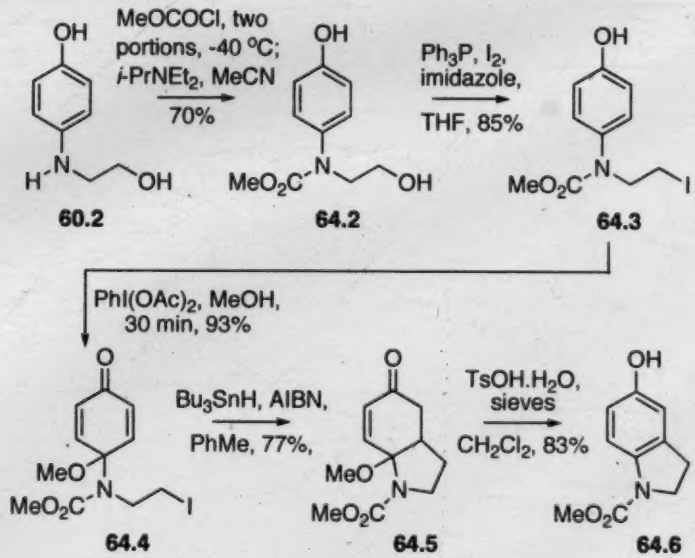
We attempted to generated the quinone imine **63.6** by removal of the alloc group, as this iodide (**63.6**) may allow synthesis of **57.3**. Treatment of **63.2** with a catalytic amount of Pd(0), as used in a transformation reported by Myers *et al.*,[57c] provided two substances (according to the ^{1}H NMR run on the crude reaction product). The minor product (^{1}H NMR) was isolated and proved to have the structure **63.5**, but the major compound was not recovered after chromatography. Myers was working on a much more complex system and we suspect that some features of that relatively large structure may stabilize the resultant quinone imine. It is likely that **63.6** is the major product, based on analogy to Myers' results and also on mechanistic grounds. We have not followed up this possibility. Perhaps a different isolation procedure would allow us to obtain **63.6** as a pure substance.



Scheme 63

As shown below, the use of methyl carbamate protection was also successful (Scheme 64). The conversion of **60.2** to **64.2** worked well when 0.6 equiv. of methyl

chloroformate was added to the starting material at -40 °C, followed by a short warming period, addition of base (0.6 equiv.), and then addition of another portion of the chloroformate at -40 °C. Formation of iodide **64.3** was then readily accomplished using an excess of our standard reagents. The oxidation, radical cyclization, and rearomatization steps (**64.3** → **64.4** → **64.5** → **64.6**) all worked well.



Scheme 64

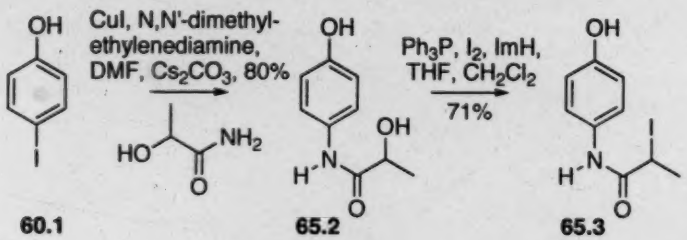
The above results show that use of alloc or methyl carbamate protection allows an efficient six-step sequence that converts unprotected iodophenols into the rearomatized products.

(b) Cross-Coupling of Primary Amides and Oxidation of Secondary p-Amidophenols

The extension of our method to compounds requiring the oxidation of secondary amides was also investigated. Fleck, Hobart and Morrow had reported[58] that a secondary *p*-

amidophenol could be oxidized. Further, Buchwald has selectively coupled amides — in the presence of amines and alcohols — to aryl iodides.[60] The combination of these methods, together with radical cyclization and rearomatization promised to provide a variety of structurally complex benzo-fused heterocycles.

Buchwald's work on copper-mediated coupling of aryl halides and amides uses a wide array of solvents and bases, and also several different ligand systems. While it was not at all obvious which combination would be best in our case, the rather arbitrarily selected conditions (CuI, *N,N*-dimethylethylenediamine, Cs_2CO_3, DMF), worked very well. Phenol **60.1** can be coupled with (*S*)-(-)-lactamide to provide **65.2**[61] (80% yield) in 2 h at 65 °C. Conversion to iodide **65.3** was accomplished using the now standard excess of reagents (imidazole, Ph_3P, I_2, 71%). The oxidation of **65.3**, readily expected by analogy to Morrow's reported oxidation, could not be achieved using $PhI(OAc)_2$. TLC analysis of the reaction mixture suggested that a product was being formed, but that it had decomposed on workup.

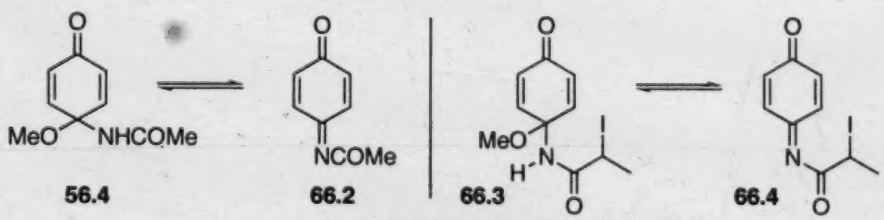


60.1 **65.2** **65.3**

Scheme 65

We examined the reported transformation **56.3** → **56.4** as a model for the oxidation of **65.3**. Using Morrow's conditions, this experiment does not work in our hands. Dr. Morrow had noted (personal communication) that some of his students found the reaction difficult to perform, and he kindly recommended another procedure; unfortunately, this also did not work. Dr. Morrow then recommended a procedure involving the direct precipitation of the product from the reaction mixture. This procedure did not work at all well, but during

one attempt, a small amount of material had stuck as a solid to the side of the flask. Analysis of this solid established that it was **56.4**. We also observed the decomposition of **56.4** in $CDCl_3$. Eventually, we developed a reliable working modification of Morrow's experiment. After the reaction is complete (TLC) the mixture is concentrated (but not to dryness) and then chromatographed directly using an eluant containing MeOH. This procedure allows **56.4** to be isolated in 75% yield. Compound **56.4** is stable as a solid and also when in the presence of both acid and MeOH. In other states the material appears (^1H NMR and TLC analysis) to exist in equilibrium with what we assume to be compound **66.2**. This observation led us to develop a modified procedure, where an apparent equilibrium between **66.2** and **56.4** is generated directly by using iodosylbenzene as the oxidant (producing H_2O instead of AcOH as a byproduct). Addition of catalytic $TsOH.H_2O$ after oxidation is complete (TLC) pushes the equilibrium toward **56.4**, which is then isolated as before. Using this procedure, **56.4** could be obtained in 92% yield. Application of this procedure to the oxidation of **65.3** provided **66.3** in 75% yield. We could not isolate **66.4** or **66.2** despite making several attempts.



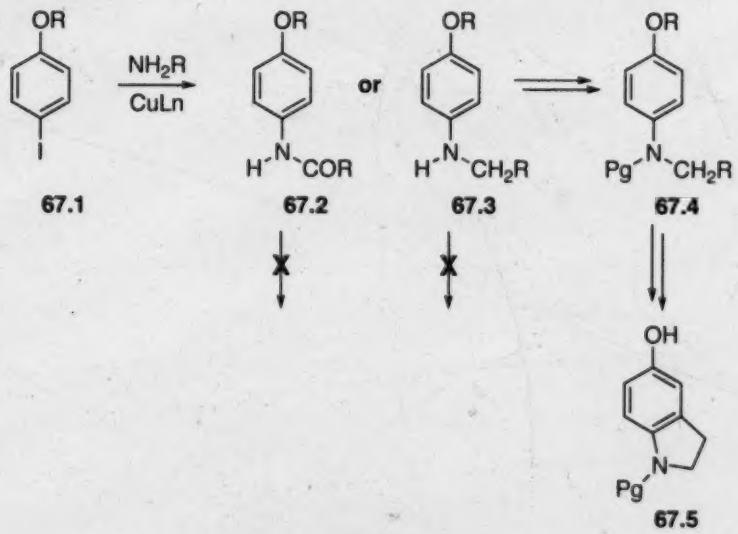
Scheme 66

With **66.3** in hand, we attempted the radical cyclization under conditions that we thought may allow cyclization to occur while stabilizing the starting material (addition of Bu_3SnH and AIBN in MeOH to a hot solution of **66.3** and cat. $TsOH.H_2O$ in MeOH). The product that was obtained in *ca* 50% yield was amide **65.3**. It seems likely that the problems in this series stem from the presence of the NH group in **56.4** and in the more

complex amide **66.3**. Analogs of compound **66.3** that are *N*-alkylated may be less problematic, but we have not yet investigated such compounds.

(c) Cross-Coupling of Protected Secondary Amino- and Amidoalcohols and Subsequent Manipulation

As summarized in Scheme 67, the work described above relies on coupling iodophenols or *O*-protected iodophenols (**67.1**) and primary amides (providing **67.2**) or amines (to give **67.3**). Although amides **67.2** and some amines **67.3** were found to undergo dearomatizing oxidation, we were unable to transform such species into benzo-fused heterocycles. A successful sequence relied on the formation of protected amines **67.4**, which could then be elaborated, in some cases, to **67.5**. Coupling of secondary amides to **67.1** would provide a direct route to **67.4**, and this approach would be more convergent and allow convenient access to additional substrates needed for our investigations.

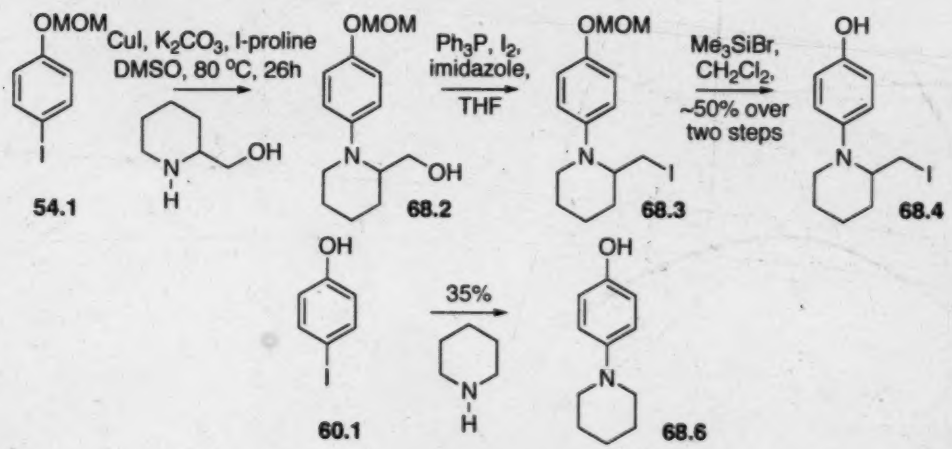


Scheme 67

In the work of both Ma and Buchwald, secondary amides or amines are reported to

couple less efficiently than their primary counterparts. The coupling of secondary amines or amides typically involves lower yields and/or higher temperatures and/or longer reaction times. This effect seems to be at least partially steric in nature, as cyclic amides and amines are not nearly as strongly affected.

A brief examination ruled out the use of dialkyl amines in our process. We chose to explore the use of secondary amines in the coupling reactions, and chose the commercially available 2-piperidinemethanol. Using Ma's conditions, the reaction **54.1** → **68.2** was found to be slow (2 equiv. amine, 80 °C, 26 h) and low-yielding (28%). Replacement of the hydroxyl by an iodide and deprotection (**68.2** → **68.3** → **68.4**) were, as usual, fairly efficient (41% over two steps). Oxidation of **68.4** failed, however. It appears that **68.4** is consumed, but no product could be isolated or even observed to form. This result with cyclic *N*-dialkyl compounds is consistent with a model study on the simpler piperidine derived **68.6**, which also disappeared when oxidation was attempted.

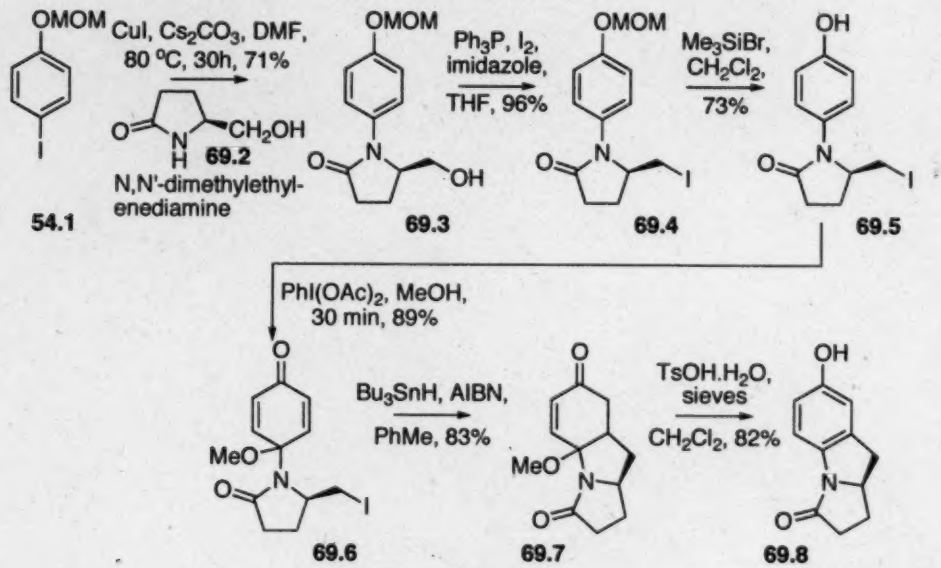


Scheme 68

The use of secondary amides was also explored. Coupling of **54.1** with the alcohol **69.2**, derived from pyroglutamic acid, provided the internally protected **69.3** (71%) when using our arbitrary version of the Buchwald conditions. Two more steps provided the cyclic

amidophenol **69.5**, made by conversion of **69.3** to iodide **69.4** (96%), followed by phenol deprotection (73%).

In all of our successful oxidations a carbonyl group is attached to the nitrogen. However, the presence of the carbonyl does not necessarily ensure that the oxidation



Scheme 69

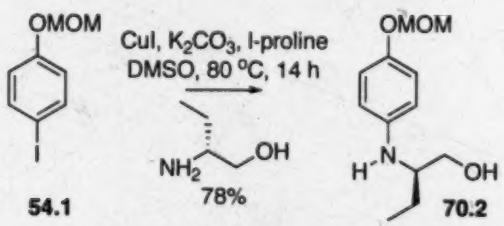
process will work (*cf.* **61.3**, Boc protection), is facile (*cf.* **54.5** → **59.2**, CF_3CO protection), or that the product will be sufficiently stable for further elaboration (*cf.* attempted cyclization of **66.3**). If successful oxidation depends on the electronic environment of the nitrogen atom, it could be anticipated that the present case (**69.5**) should be an intermediate example between the relatively electron-rich nitrogen atoms of methyl- and allyl carbamates, and the more electron-deficient trifluoroacetoxyamide **54.5**. In the event, oxidation of **69.5** → **69.6** proceeded well (89%). The radical cyclization **69.6** → **69.7** also gave a good yield (83%), and the aromatization of **69.7**, using our optimized conditions, provided **69.8** in 82% yield.

The ease of all the transformations used to convert **54.1** into a tricyclic amide (**69.8**)

suggests that this method may be suitable for more elaborate substrates. The convergent nature of the transformation **54.1** → **69.3** would certainly facilitate the use of this process in complex molecule construction. In making **69.3** we used an arbitrary set of conditions that were based on Buchwald's observations; in principle, optimization of these conditions may also allow the use of unprotected phenols in this already short sequence.

2.4.5 Synthesis of Substituted Dihydroindoles

To explore the formation of substituted *N*-heterocycles, we used an amine with ethyl substitution. As the amino group of 2-amino-1-butanol is more hindered than the hydroxyl, we anticipated that the coupling reaction might be problematic, and so we used MOM protection of the iodophenol. In the event, the coupling **54.1** → **70.2** proceeded in good yield (78%, Scheme 70) when the reaction was conducted at 80 °C for 14 h. Conversion of **70.2** into the requisite *N*-protected iodide was not a straightforward process, however.



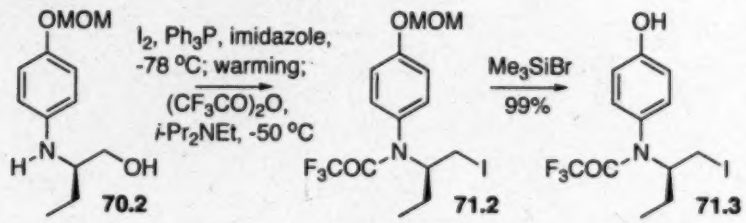
54.1 **70.2**

Scheme 70

Direct conversion to the amino iodide (Scheme 71) was complicated by various side reactions, possibly derived from aziridine formation and then opening of the three-membered ring. The addition of excess reagents (I_2, Ph_3P, imidazole) to a cold (-78 °C) solution of **70.2**, followed by removal of the cold bath, greatly suppressed this problem, and the resulting material was promptly protected as the trifluoroacetoxy amide **71.2**.

Compound **71.2** (obtained in 94% yield over two steps) is unusual as it appears to be either two different substances or one compound that exists as a 1:1 mixture of two

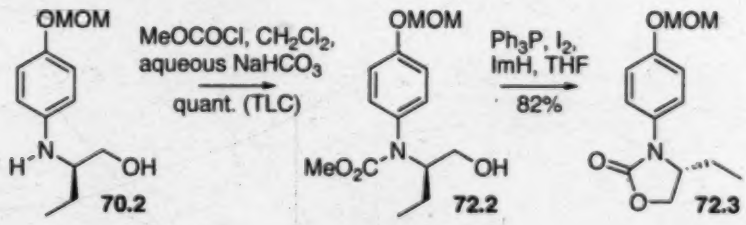
rotamers. The ^{1}H and ^{13}C NMR data suggest that there is only one MOM unit in the product(s) but, unfortunately, variable temperature NMR experiments were inconclusive. Deprotection gave what we hoped was **71.3** (99%), which still appeared as two distinct rotamers. The oxidation of **71.3** did not proceed cleanly. At 0 °C, when using $PhI(OCOCF_3)_2$ as the oxidizing agent, the material that could be isolated in 53% yield had MS data that was consistent with the desired structure, and the NMR data appeared to be compatible with the presence of a mixture of diastereoisomers, each of which was a mixture of rotamers. These interpretations are highly speculative, as the spectra, like most we have examined in the nitrogen series, are very complicated.



Scheme 71

An attempt was made to oxidize **71.3** (if that be the structure) electrochemically. Such oxidation would generate acid, and so we chose to use sodium acetate as the electrolyte. No reaction, even at a high voltage,[62] was observed.

An attempted one-pot sequence of radical cyclization and rearomatization on the material described above from attempted chemical oxidation of **71.3** gave no trace of the



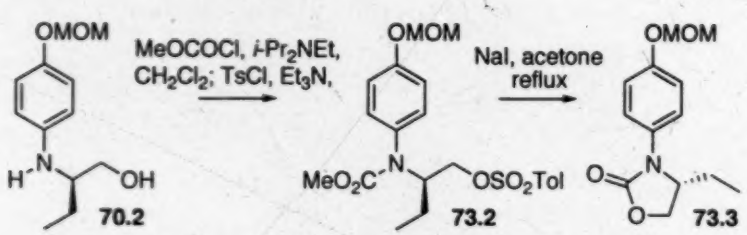
Scheme 72

desired final product. Consequently, the oxidation was not explored further.

As discussed in Section 2.4.4-a, we had developed an alternative sequence that involves *N*-protection *before* iodide formation; but, in the present case, this route was also problematic. While quantitative conversion (TLC) of **70.2** to **72.2** was observed, exposure of this material to Samuelson's conditions provided cyclic carbamate **72.3** instead of the desired iodide.

The formation of **72.3** is due to the sensitivity of the carbamate carbonyl to electrophilic activation of the hydroxyl group; similar reactivity had been observed earlier in an example involving Boc protection (**61.2** → **61.4**). Ethyl substitution of the alkyl chain may favor a conformation that leads to this intramolecular displacement in the case of MeOOC protection; in the absence of substitution this complication does not arise (*cf.* **64.2** → **64.3**). To circumvent formation of a highly reactive $ROPPh_3$ intermediate, an approach involving Finkelstein displacement of a tosylate was tried (Scheme 73).

A one-pot procedure involving selective *N*-protection of **70.2** and then tosylation proceeded smoothly to give **73.2**, although no yield was measured. Treatment of **73.2** with NaI gave **73.3** quantitatively (^{1}H NMR).

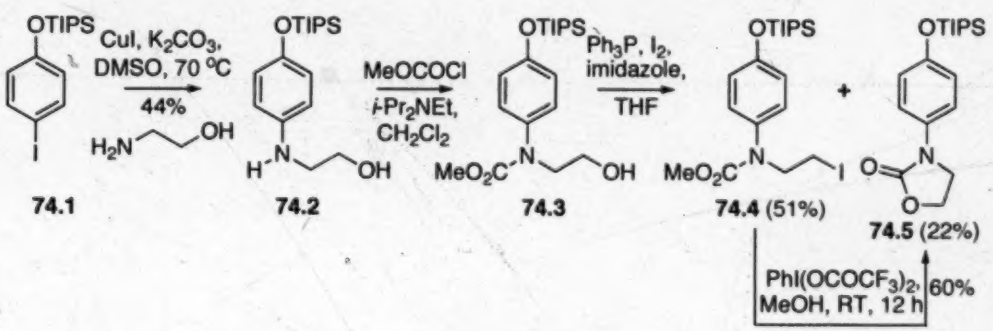


Scheme 73

It appeared that these carbamates are not compatible with certain reaction conditions and/or functional groups. Another case illustrating the sensitivity of carbamates is shown in Scheme 74.

That sequence starts with TIPS-protected phenol **74.1**. Ma's coupling conditions

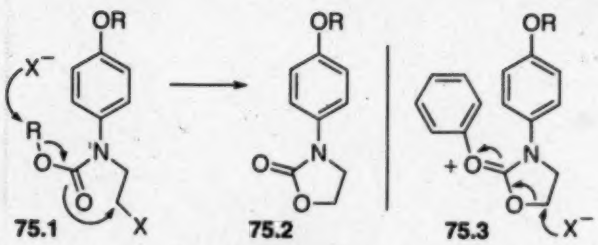
were found to partially remove the TIPS group, but it is possible that optimization may allow us to suppress this side reaction. Chemoselective protection of the desired coupling product (**74.2**) as a methyl carbamate was followed by conversion to the iodide (**74.3** → **74.4**, 51% yield over two steps). Formation of iodide **74.4** was accompanied by the cyclic carbamate **74.5** (22%, two steps). We attempted to perform a one-pot deprotection-oxidation sequence on **74.4** in a bid to obtain directly the cross-conjugated ketone **64.4** (Scheme 64). Treatment of **74.4** under standard oxidizing conditions gave **74.5** and no oxidation product. We were also unable to deprotect and oxidize **74.5** in a one-pot sequence. Product **74.5** likely arises from activation of the halogen by the oxidizing agent.



Scheme 74

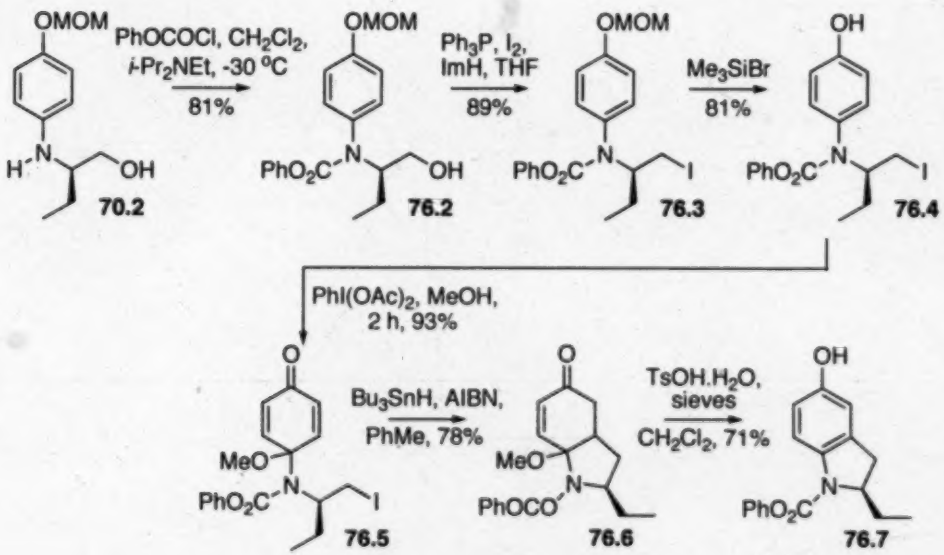
These decomposition pathways leading to cyclic products are probably facilitated by the irreversible loss of the alkyl group on the carbamate (see **75.1** → **75.2**, Scheme 75). The use of a carbamate which could not undergo loss of the alkyl group by an S_N1, S_N2 or S_N2' process may not readily decompose past intermediate **75.3**. If this were the case then **75.1** might be reformed from intermediate **75.3**. The use of a phenyl carbamate in the reaction sequence was then explored.

Protection of the amide as a phenyl carbamate **70.2** → **76.2** occurred smoothly under the conditions shown (81%). Treatment of phenyl carbamate **76.2** with an excess of the iodination reagents allowed smooth conversion to **76.3** in 89% yield — a result



Scheme 75

consistent with the mechanistic interpretation of Scheme 75. Deprotection to phenol **76.4**was also straightforward (81% yield). The oxidation occurred readily, but isolation of **76.5** was accompanied by extensive decomposition, and a black tar was obtained in the first few runs. The compound is actually stable to a large number of conditions but decomposes rapidly when its solutions are concentrated to dryness, even when protected from light. It is best to expose **76.5** to oil pump vacuum for no more than a few seconds, and certainly less than 1 min.



Scheme 76

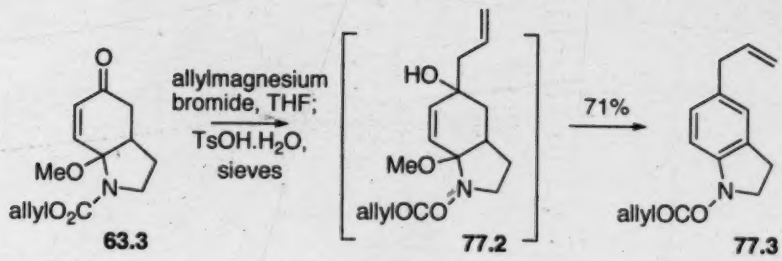
Radical cyclization of material prepared this way was found to produce a stable ketone (**76.6**), which was readily aromatized to **76.7**.

Despite extensive efforts we were not able to apply our method to the case of *t*-butyl substitution. The coupling reaction of **54.1** (*cf.* **54.1** → **70.2**) with *t*-butyl leucine proceeded in low yield and formation of the coupled product appeared to stop after *ca* 35% conversion. The yield was improved to 48% after correction for recovered starting material. Possibly, this result could be improved by using an excess of the amino alcohol. Conversion to the amino iodide (*cf.* Scheme 71) was unsuccessful, even though a number of procedures were examined in which we attempted to trap the amino iodide by *N*-acylation. Selective protection of the amine moiety (*cf.* **70.2** → **72.2**,) in the presence of the free hydroxyl was also unsuccessful; *carbonates* were formed instead of *carbamates*. These experiments were done before the successful reactions on ethyl substitution described above, and the use of phenyl carbamate protection (*cf.* **70.2** → **76.2**) had also not yet been developed, but probably selective *N*-protection would have been impossible here too. A procedure involving selective protection of the alcohol (by silylation), followed by phenyl carbamate formation and then deblocking of the alcohol was not explored but is, in hindsight, a sequence that should have been studied. When we treated the amino alcohol with an excess of a chloroformate the hydroxyl was acylated first, followed by the nitrogen, and attempts at selective base-hydrolysis showed that the *N*-acyl group was removed more readily.

2.4.6 Manipulation of the Radical Cyclization Products before Aromatization

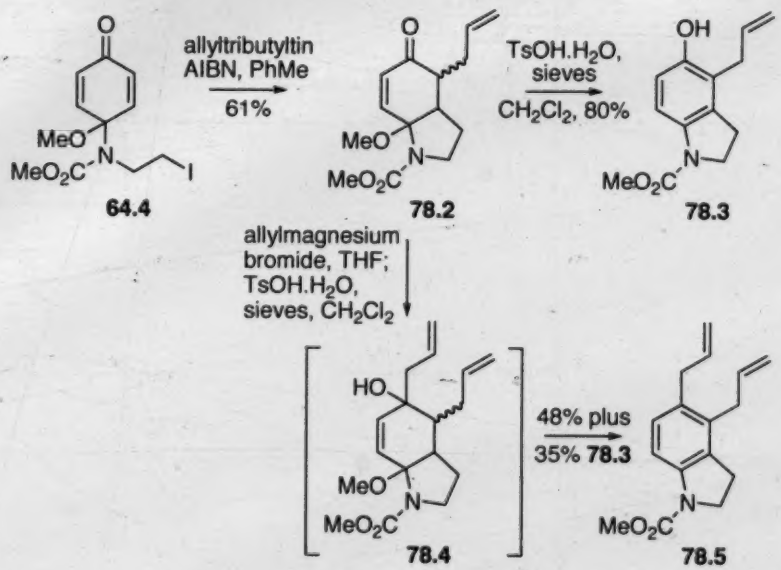
The present method can be modified to generate compounds carrying a carbon substituent instead of a phenolic hydroxyl (Scheme 77, **63.3** → **77.3**). It is anticipated that, as in the oxygen work, the usual hydroxyl group can also be replaced by a hydrogen.

Another modification is that the intermediate radical arising from the closure step can be trapped to provide 1,2,3,4-tetrasubstituted products. This was done in the case of



Scheme 77

iodide **64.4** (Scheme 78). When the iodide was heated with allyltributyltin and AIBN, Keck allylation occurred after ring closure to give **78.2** in 61% yield. A large amount of silica gel was required for chromatographic purification of **78.2**, and a one pot transformation (**64.4** → **78.3**) may provide a higher overall yield. When **78.2** was treated with acid and molecular sieves phenol **78.3** was formed efficiently (80%).



Scheme 78

Both of these modifications, interception of the intermediate radical and addition of a Grignard reagent, can easily be combined with a single substrate (Scheme 78, **78.2** → **78.4**

→ **78.5**). A single experiment of this type was performed which involved the addition of 1.2 equiv of allylmagnesium bromide to **78.2**. Evidently this was not an adequate amount for complete conversion to **78.4** since, after aromatization **78.5** (48%) was accompanied by a substantial amount of **78.3** (35% yield).

These processes provide products that are functionalized to allow further elaboration. It is likely that other radical trapping reagents (*cf.* **64.4** → **78.2**) and nucleophilic species (*cf.* **78.2** → **78.4**) can be employed to provide a range of products.

3 CONCLUSION

Although a considerable amount of work remains to be done, we have been able to illustrate a general approach to oxidative radical cyclization onto a benzene ring so as to form benzo-fused oxygen and nitrogen heterocycles. Extension to carbocycles is an obvious next topic.

Our chief requirement was that the method operate under standard radical cyclization conditions, and this has been achieved through a procedure that relies on performing the oxidation step first.

The method allows the formation of five, six and seven-membered oxygen heterocyclic rings fused to phenols. We have developed modifications allowing construction of non-phenolic aromatic species and/or the introduction of alkyl or aryl substituents on the aromatic ring.

The method is a very effective route to benzo-fused oxygen heterocycles (Section 2.2) and gives access to substitution patterns not easily accessible by other methods. Additionally, dihydrobenzofurans are not available by Zard's radical xanthate method (Scheme 22), and very low yields are observed when making biaryl oxygen heterocycles by other radical procedures (*cf.* Scheme 10).

Our method was applied to the synthesis of a sensitive natural product (*ent*-nocardione A), as described in Section 2.3. The procedure overcomes the previously

illustrated limitations in construction of substituted benzo-fused dihydrofuran rings by known methods, and a ten-fold overall yield increase was realized over Mori's synthesis of optically pure nocardione A.

The exploratory synthetic work discussed in Section 2.3 allows extension to the synthesis of nitrogen heterocycles. A number of possibilities were explored, and while they were not all successful, overcoming these synthetic challenges guided the development of useful sequences. The method appears to be a flexible and general route to a wide range of benzo-fused nitrogen heterocycles. The results in this section also significantly expand what was known about the oxidation of *p*-aminophenols. The use of phenyl carbamates provides a practical solution to the problem of forming substituted dihydroindoles, and this protecting group may be the key for extension to more complex substrates. This work enables us to explore the synthesis of enantiomerically pure benzo-fused substituted *N*-heterocycles by starting with optically pure amino alcohols. A general method to such structures is currently not available.

4 FUTURE RESEARCH

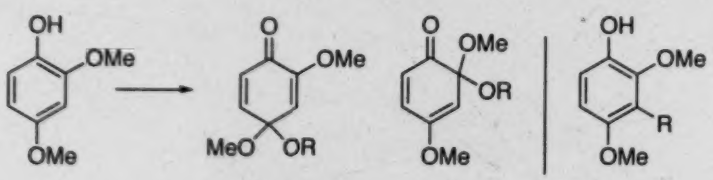
4.1 Formation of Benzo-fused Oxygen Heterocycles

Another member of our group, Dazhan Liu,[39] has expanded the work of Section 2.2 by changing the substitution patterns of the starting phenols. This work[39b] by Mr. Liu illustrates that the general oxidative radical cyclization process is satisfactory when an additional methoxy substituent is present. What other substituents are tolerated has not yet been established.

The outcome of the series when a methoxy substituent is *ortho* to the phenolic hydroxyl should be examined. If a dimethoxy species such as **79.1** were oxidized, a mixture of regioisomers (**79.2** and **79.3**) might be formed. Additional substitution between the methoxy substituents (*cf.* **79.4**) may favor formation of cross-conjugated ketones **79.2**.

4.2 Application via ortho-Oxidation

In all systems examined thus far, oxidation of a *para*-substituted phenol gave cross-conjugated dienones. The *ortho*-oxidation process is known,[63] but it is often complicated because the resulting 1,3-dienes (*cf.* **80.2**) undergo Diels-Alder reactions to give dimers. This side reaction is suppressed by an electron-withdrawing substituent on the phenol ring.[64] The application of our methodology would provide substitution patterns not available by our earlier work. Issues that will need to be addressed include the nature of permanent and removable electron-withdrawing groups; a bromine atom *para* to the phenolic hydroxyl is reported to work well,[65] but this might adversely affect the radical cyclization. The optimum position of the electron-withdrawing substituent on the ring is also not clear.

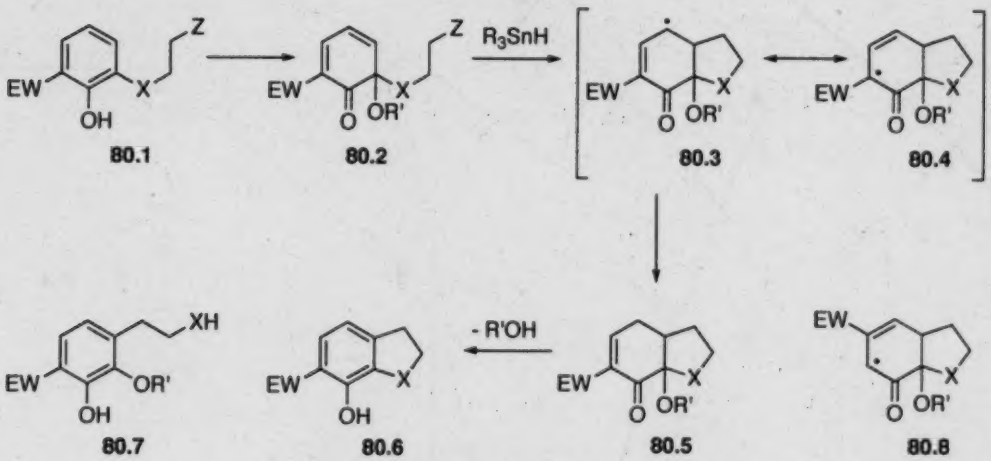


79.1 **79.2** **79.3** **79.4**

Scheme 79

The position chosen for the electron-withdrawing group (*ortho* to the phenolic hydroxy) in **80.1** allows conjugation of this group with the radical generated in the cyclization process (*cf.* **80.3**, **80.4**). Our working examples involve cross-conjugated species, and the conjugated nature of the unsaturated system in **80.3** and **80.4** may stabilize the radical. If this is so, it could adversely affect the propagation step where a hydrogen atom is abstracted from a stannane (**80.3** → **80.5**). Moving the electron-withdrawing group to the *meta* position as shown in **80.8** might avoid this problem. The addition of catalytic PhSeSePh has been reported to facilitate hydrogen atom transfer in difficult cases and we can apply this technology if necessary.[3] Presumably hydrogen atom donation to the intermediate radical will occur preferentially as shown in **80.3** → **80.5**. This would provide

a conjugated product, but access to the radical position illustrated in resonance form **80.4** is also sterically blocked by the electron-withdrawing group.



Scheme 80

By analogy to our earlier work, rearomatization is expected to give **80.6** rather than **80.7**.

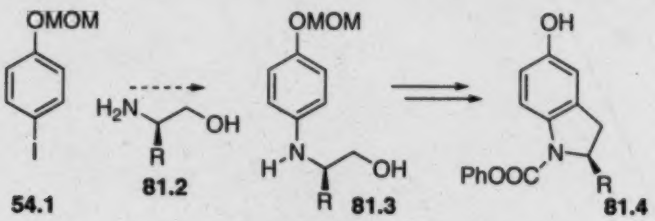
This process of *ortho* oxidation is probably best explored in the case of *ortho*-alkoxy phenols, which would provide benzo-fused oxygen heterocycles. The oxygen series involves a more developed and predictable oxidation process, and the oxidation precursors are also more readily available.

4.3 Formation of Benzo-Fused Nitrogen Heterocycles

Considerable work still needs to be done to define the scope and limitations of our method for oxidative radical cyclization in the nitrogen series.

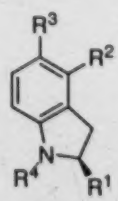
The most valuable aspect of this methodology is the possibility that we will be able to fuse an optically pure amino alcohol (**81.2**) to the benzene ring in the sense shown in Scheme 81. As illustrated in Section 2.4.5, a sequence involving substituted amino alcohols

was initially problematic. However, the use of phenyl carbamate protection (Scheme 76) allows these transformations to be carried out. It is anticipated, from the mechanisms of the reactions that will be used to convert **54.1** into heterocycles, that no racemization will occur. The use of unprotected phenols in this sequence has not yet been explored.



Scheme 81

In principle, the use of different amino alcohols **81.2**, could be combined with our procedures for manipulation of the normal sequence (Section 2.4.6) to make a large number of optically pure substituted dihydroindoles (*cf.* **82.1**). In this case R^1 is the substituent from the amino alcohol, R^2 is hydrogen or a substituent derived from trapping the intermediate radical, R^3 can be H, OH, aryl or alkyl, and R^4 is derived from manipulation of the amine moiety. The use of substituted aryl iodides instead of **54.1** may also be practical.



Scheme 82

The assumed generality of phenyl carbamate protection in these sequences will need to be confirmed. David Wingert, another member of our group, has used phenyl carbamate

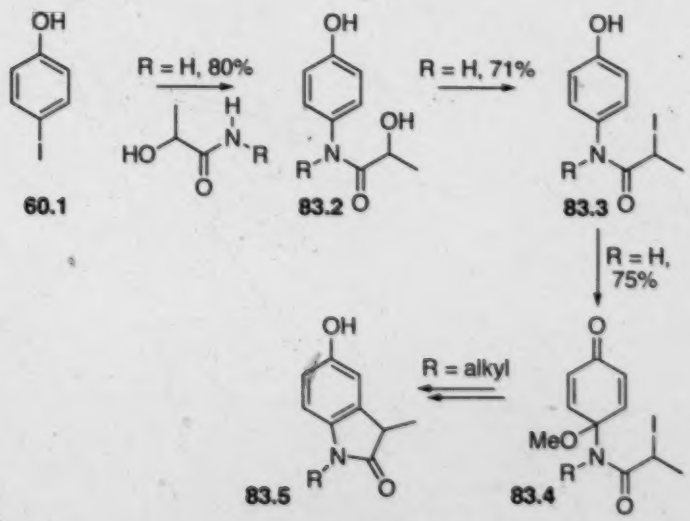
protection in an unsubstituted series.[66a] These experiments also confirmed that the phenolic hydroxyl can be replaced by a hydrogen atom or an aryl group (*cf.* Section 2.4.6) in the nitrogen series.

The use of non-cyclic secondary amides (*cf.* Scheme 69) in sequences involving Buchwald's coupling procedure is a potentially useful possibility that should be explored further.

Another important extension of the method will be the synthesis of higher homologues of dihydroindoles. Based on analogy to oxygen-containing heteroaromatic systems, we should be able to make six- and seven-membered rings. If these processes are successful we will next explore the use of *substituted* three- and four-carbon chain amino alcohols in our sequence.

Jianbiao Peng,[66a,b] another member of our group, is exploring the sequence to make benzo-fused six-membered *N*-heterocyclic rings. He has found that the unsubstituted example is successful, and work on substituted variations is in progress.

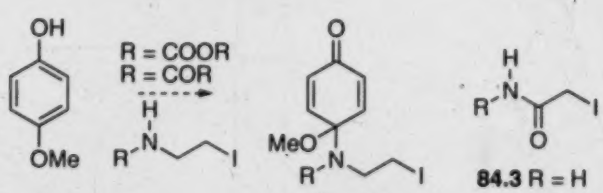
A sequence that would have given dihydroindolinone products was attempted (see



Scheme 83

Section 2.4.4-b). As shown in Scheme 83, the sequence involving a primary amide was successful through the coupling (**60.1** → **83.2**), functional group interconversion (**83.2** → **83.3**), and oxidation (**83.3** → **83.4**) stages. However, when R was hydrogen the radical cyclization was unsuccessful. This result may have been due to the presence of the secondary amide group, which rendered **83.4** unstable to various conditions. If this is correct, then converting R to an alkyl group before coupling or at any other stage would solve the problem, although these processes may not be straightforward.

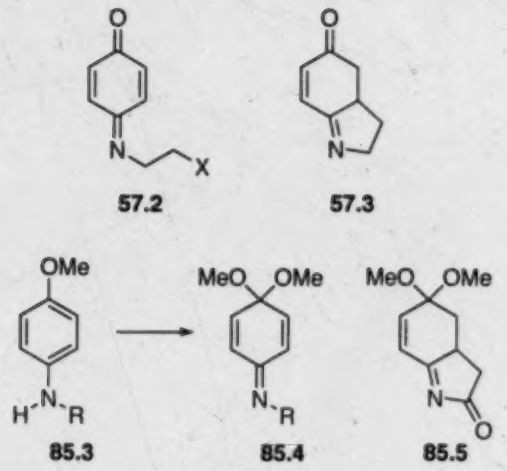
We have not yet explored the direct oxidative coupling of *p*-alkoxy phenols with amides or carbamates along the lines shown in Scheme 84. Oxidations would presumably best be done in non-nucleophilic polar solvents known to be compatible with hypervalent iodide oxidations, such as MeCN or CH_2Cl_2, although the use of 1,2,3-triflouroethanol or hexafluoro-2-propanol, as developed by Kita,[67] may be necessary. Amido iodides may not be appropriate substrates for this sequence, but in this case the use of chlorides or protected alcohols would be explored. Compound **84.3** is commercially available, and its use (or, more likely, the use of an *N*-alkylated derivative) in such an oxidation may allow dihydroindolinone synthesis to be accomplished.



34.1 **84.2** **84.3** R = H

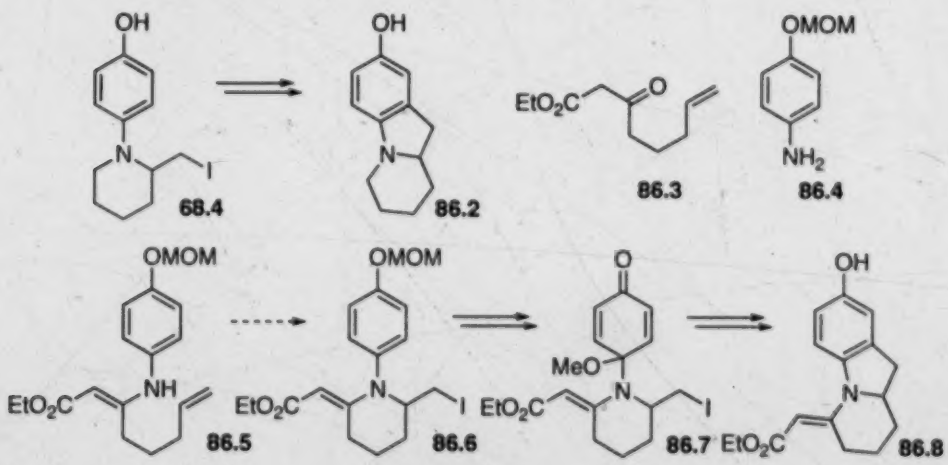
Scheme 84

Despite several attempts (described in Section 2.4), we were unable to generate quinone imines such as **57.2** (except where X = OTs) (note that **57.2** is a tentative structural assignment), and explore cyclization to molecules such as **57.3**. A potentially useful alternative sequence, **85.3** → **85.4**, is known to be facile when an electron withdrawing



Scheme 85

substituent is on the nitrogen atom.[68] The use of **85.4**, where R incorporates both a homolyzable group and an electron withdrawing moiety attached to N may allow radical cyclization, leading to compounds such as **85.5**.



Scheme 86

The oxidation of tertiary dialkyl substituted amines failed in our hands (*cf.* **68.4**, Section 2.4.4-c) and thus we could not synthesize tricyclic amines such as **86.2**. A practical

solution to this problem may be the use of vinylogous carbamates such as **86.6**. Such compounds may be electronically similar to the amides and carbamates that underwent our oxidative radical cyclization, and the products (**86.8**) would be amenable to further manipulation.

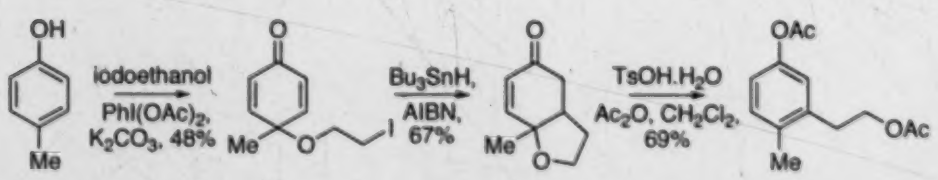
The coupling of ketoesters such as **86.3** with amines is known to provide the unsaturated moiety present in **86.5**, rather than imines. Iodoamination of **86.5** would provide **86.6**,[69] which may undergo oxidation after deprotection of the phenolic oxygen. This sequence would provide a class of nitrogen heterocycles currently unavailable by our method. The approach would complement our current cross-coupling strategy and still be highly convergent.

4.4 Application of the General Method to Compounds Requiring the Oxidation of p-Alkylphenols

All of the above work involves the use of a phenol that is substituted with a heteroatom (*cf.* **31.1**, X = NR, O). A challenge that has to be dealt with is the use of carbon substituents in our general procedure, where X = CR^1R^2.

4.4.1 A Formal Method for meta-Alkylation

We have examined an oxidation where a methyl group *para* to the phenolic hydroxyl is tolerated, although in the single example the yield in the oxidation step (**87.1** → **87.2**) was only 48%. To achieve this yield freshly purified *p*-cresol was required. The oxidation in the presence of chloro alcohols was not examined. The process in Scheme 87,



87.1 **87.2** **87.3** **87.4**

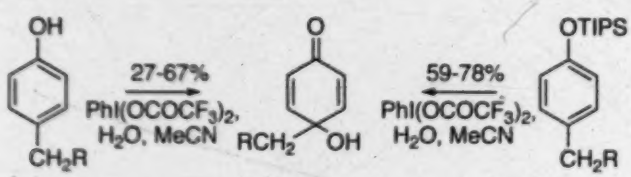
Scheme 87

if general, could serve as a formal method for *meta* alkylation of a phenol.

In this case there is no methoxy group to expel, and so the heterocyclic ring opens on rearomatization (**87.3** → **87.4**). This aromatization was initially problematic, and the expected phenol could not be isolated. However, *in situ* acetylation, achieved by acid treatment in the presence of Ac_2O, delivered acetate **87.4** in 69% yield.

It may be worth exploring the generality of this process; the yields are low at present, but the sequence is only three steps.

The general oxidation process shown in Scheme 88 is reported to be more efficient when the phenol is masked as a silyl ether.[70] Here the deprotection and oxidation occur in one pot. It is possible that the deprotection requires the presence of water to remove the



88.1 **88.2** **88.3**

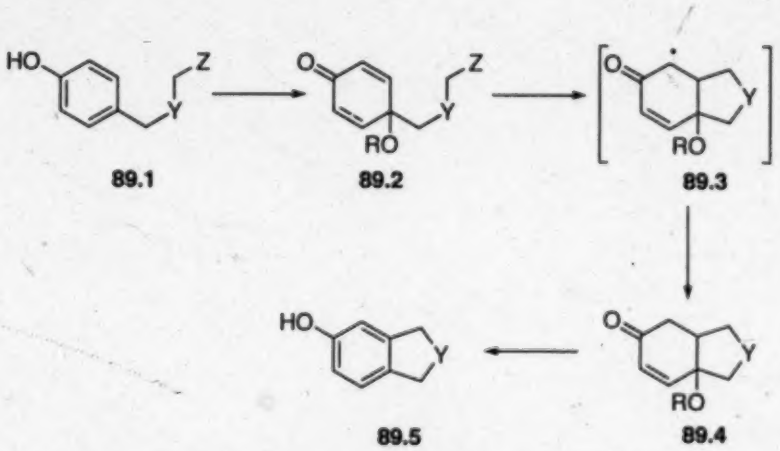
Scheme 88

TIPS group (*cf.* the unsuccessful attempt to oxidize **74.4**). If water is necessary then this technique could not be applied to the alkylation method of Scheme 87, because it has been shown that, in related oxidations, water is a much more effective nucleophile than MeOH.[71]

It may be worthwhile to optimize the reaction conditions used in the oxidation **87.1** → **87.2**. The addition of a non-nucleophilic cosolvent and/or use of a different oxidizing agent may improve this process. A supermolecular complex of PhIOH and 18-crown-6 was recently reported to oxidize 2,4,6-trimethylphenol to a *p*-quinol in 92% yield, but the generality of the new reagent is not yet established.[72] The yields of *p*-alkylphenol oxidations have also been reported to increase significantly when polymer supported reagents are used.[73]

4.4.2 Synthesis of Benzo-Fused Carbocycles

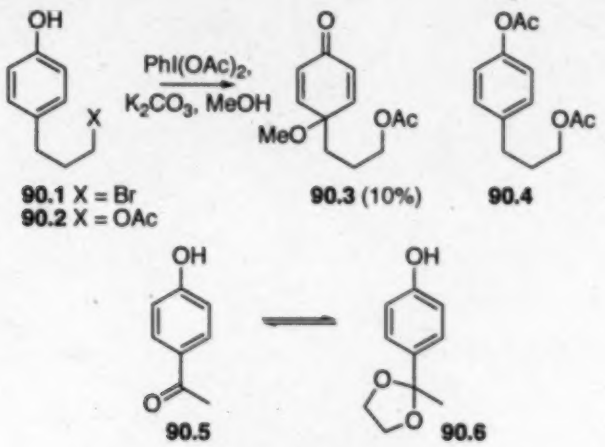
To use our oxidative radical cyclization to generate a carbocyclic ring (**89.5**) the oxidation **89.1** → **89.2** is required. While we have briefly explored this, the work needs to be reexamined.



Scheme 89

We attempted to capture the product of phenol oxidation with MeOH, rather than water, and we used oxidation conditions optimized for *p*-alkoxy phenols. Oxidation of **90.1** provided a complex mixture of products, but acetate **90.2** could be oxidized to **90.3** in about 10% yield. Attempts to improve this yield by *in situ* deacylation and oxidation of **90.4** also led to a complex mixture. Side reactions in the oxidations of **90.1**, **90.2**, and **90.4** were believed to be caused by the presence of benzylic protons, and so compounds which lack these protons (**90.5** and **90.6**) were examined. Attempted oxidation of **90.5** provided only recovered starting material, and we did not try other conditions. It should be noted that the oxidation of a *para*-amino phenol failed in the presence of base (**55.4** → **57.2**). To examine the oxidation of a more electron-rich substrate, we attempted to generate **90.6** [$HC(OMe)_3$, $TsOH.H_2O$, PhMe or CH_2Cl_2], but found that **90.6** exists in equilibrium with **90.5** and decomposes upon isolation. Formation of **90.6**, followed by oxidation without

isolation, using MeOH as the solvent, looked promising (as judged by TLC monitoring of the reaction mixture), but provided a complex mixture of products upon attempted isolation.

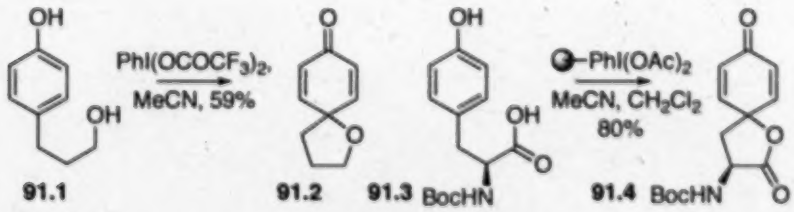


Scheme 90

Based on the apparent reactively of TIPS-protected phenols, a tandem TIPS-removal/oxidation sequence should be attempted on substrates that conform to Scheme 89. Other oxidation conditions should also be examined, particularly those that trap the oxidized phenol with water.

4.4.3 Synthesis of Benzo-Fused Medium Sized Rings

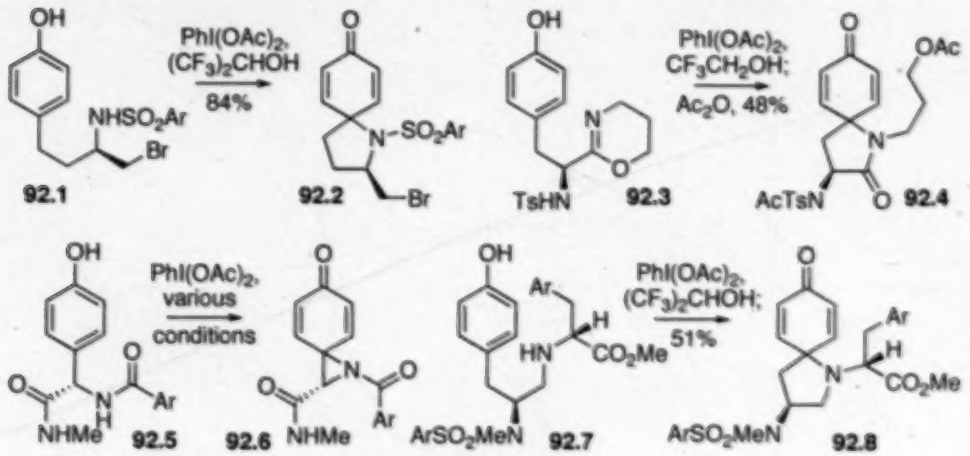
There are several reports of *para*-alkyl phenols being oxidized where the oxidation intermediate is trapped intramolecularly by a heteroatom. In the processes shown in



Scheme 91

Scheme 91 an oxygen atom is trapped.[74]

The processes shown in Scheme 92 illustrate very recent solutions to the long term problem of forming a spiro lactam or spiro amine through phenolic oxidation.[75]

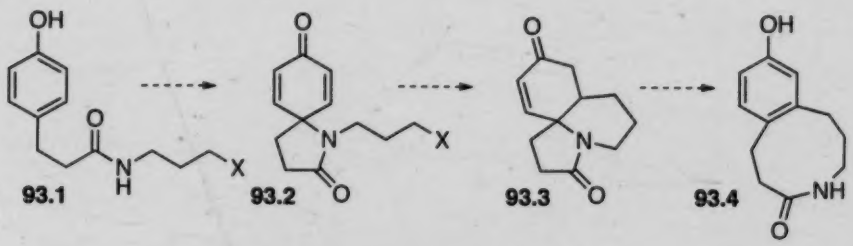


Scheme 92

Our general method for oxidative radical cyclization onto an aromatic ring is currently limited to the synthesis of five-, six- and seven-membered rings. Extension to medium-sized rings may be possible indirectly, by the incorporation of a heteroatom *into the alkyl chain* (in the sense of compound **93.1**). The heteroatom would readily trap the anion derived from phenol oxidation.

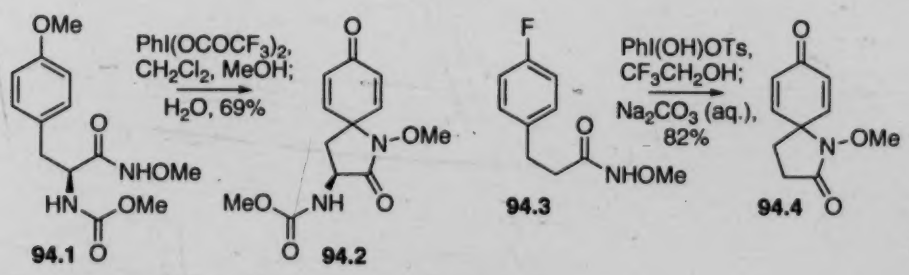
It is likely that the oxidation of **93.1** would not give **93.2** as shown, but rather products derived from trapping the oxygen atom followed by decomposition. Spiro lactones are preferentially formed over spiro lactams due to an electronic effect; resonance causes the accumulation of negative charge on the carbonyl oxygen while the nitrogen is electron deficient and rendered non-nucleophilic. A solution to this problem was recently reported by Ciufolini *et al.*[75b,c] where oxazolines are used as the synthetic equivalent of amides. Transformations such as **92.3** → **92.4** would serve as a formal oxidation of type

93.1 → 93.2. Amide nitrogen atoms have been reported to undergo a process similar to **93.1 → 93.2**, when three membered rings are formed. The oxidation of **92.5 → 92.6** was an undesired pathway reported by Ley *et al.*[75c] We should be able to make spiro-heterocycles, for example **93.2** (X = OH), by a transformation similar to that shown in **92.3 → 92.4**. In this case, radical cyclization would form a new six-membered ring, and acid catalyzed expulsion of the heteroatom in **93.3** would provide a nine-membered benzo-fused carbocycle.



Scheme 93

Spiro lactam structures are also available by the oxidation of *N*-methoxyamides. When exposed to hypervalent iodine reagents, the amide forms an *N*-methoxy-*N*-acylnitrenium ion, which is then attacked by an activated benzene ring, as shown in Scheme 94. The use of a *p*-methoxy substituent allows easy spirocylization, followed by loss of methanol to a dienone (**94.1 → 94.2**).[76] *p*-Halophenyl compounds also work well in this

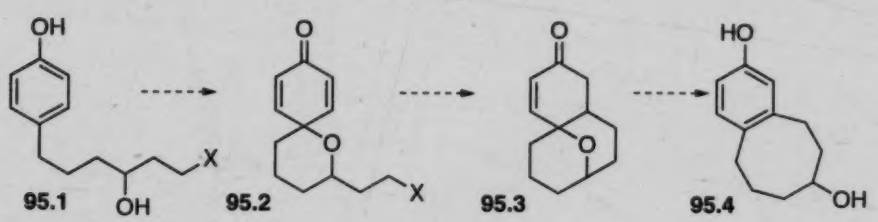


Scheme 94

process. The halogen can be F, Cl or Br and the aryl ring can also be substituted.[77]

A variety of alternative sequences that involve trapping with a heteroatom *attached to* the carbon chain (*cf.* compound **95.1** where an alcohol is used) can be envisioned. In the case shown (**95.1** → **95.2** → **95.3** → **95.4**), application of our oxidative radical cyclization method would then give an eight-membered ring.

The spiro-tricyclic intermediates that would be generated in the processes shown in Schemes 93 and 95 (**93.3** and **95.3**) may themselves serve as useful intermediates in



Scheme 95

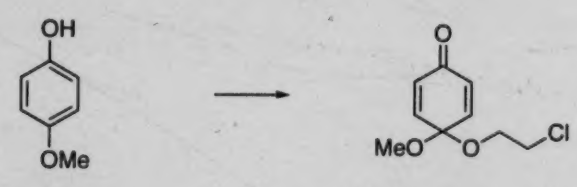
synthesis; the enone functionality is certainly suitable for further elaboration. Use of a chiral non-racemic alcohol in **95.1** → **95.2** is a variation of this process which may have useful applications.

5 EXPERIMENTAL

The same general procedures that were described in Chapter 1 apply. As before, the symbols s, d, t, and q used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively. Because of rotational restriction many of the signals were distorted, if an "m" appears before s, d, t, or q this indicates the presence of many signals in close proximity. The use of "br" indicates that the signal is simply broadened by the rotational effects.

Cu-catalyzed coupling reactions should be done at a concentration greater than 1 M. When the reaction is scaled up (> 1 g) the concentration should be lower (0.5-0.75 M).

4-(2-Chloroethoxy)-4-methoxycyclohexa-2,5-dienone (35.2).



34.1 **35.2**

$PhI(OAc)_2$ (143 mg, 0.443 mmol) and K_2CO_3 (122 mg, 0.886 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min 2-chloroethanol (1 mL) was injected and, after a further 10 min, a solution of **34.1** (50 mg, 0.40 mmol) in 2-chloroethanol (1 mL) was added dropwise over *ca* 6 min. A further portion of 2-chloroethanol (1 mL) was used as a rinse, which was added rapidly. Stirring was continued for 50 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was kept under oil pump vacuum (0.3 mm Hg) for 50 min in order to remove the excess of 2-chloroethanol. Flash chromatography of the residue over silica gel (1 x 24 cm), using 1:10:90 to 1:20:80 Et_3N-EtOAc-hexane, gave **35.2** (68 mg, 84%) as an oil: FTIR ($CHCl_3$, cast) 2962, 1689, 1674, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.39 (s, 3 H), 3.61 (t, J = 5.9 Hz, 2 H), 3.81 (t, J = 5.9 Hz, 2 H), 6.23-6.25 (m, 1 H), 6.27-6.29 (m, 1 H), 6.77-6.79 (m, 1 H), 6.81-6.83 (m, 1 H) (strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.7 (t), 50.7 (q), 60.1 (t), 92.6 (s), 130.1 (d), 142.8 (d), 184.9 (s); exact mass *m/z* calcd for $C_9H_{11}{}^{35}ClO_3$ 204.03673, found 204.03697.

4-(2-Iodoethoxy)-4-methoxycyclohexa-2,5-dienone (35.3).

35.2 **35.3**

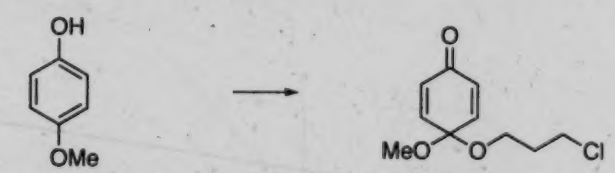
Acetone (1 mL, dried over K_2CO_3) was added into a mixture of **35.2** (37.0 mg, 0.183 mmol) and anhydrous NaI (85.2 mg, 0.568 mmol). The mixture was stirred and refluxed for 45 h, cooled and evaporated,. The residue was partitioned between water and Et_2O, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (26 x 1.2 cm), using first hexane, and then EtOAc-hexane mixtures up to 1:10 EtOAc-hexane, gave **35.3** (38.4 mg, 71%) as an oil: FTIR (CH_2Cl_2, cast) 2940, 2832, 1688, 1638, 1617, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.35 (t, J = 6.8 Hz, 2 H), 3.42 (s, 3 H), 3.84 (t, J = 6.8 Hz, 2 H), 6.25-6.32 (m, 2 H), 6.78-6.88 (m, 2 H), (strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 50.9 (q), 63.8 (t), 92.6 (s), 130.1 (d), 143.0 (d), 184.9 (s); exact mass m/z calcd for $C_9H_{11}IO_3$ 293.97531, found 293.97605. If I were to do this experiment again I would use DME as the reaction solvent, and Et_3N during the chromatography.

4-(2-Iodoethoxy)-4-methoxycyclohexa-2,5-dienone (35.3).

34.1 **35.3**

$PhI(OAc)_2$ (143 mg, 0.443 mmol) and K_2CO_3 (122 mg, 0.886 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, 2-iodoethanol (1 mL) was injected and, after a further 5 min, a solution of **34.1** (52.3 mg, 0.422 mmol) in 2-iodoethanol (1 mL) was added dropwise over *ca* 7 min. A further portion of 2-iodoethanol (0.5 mL) was used as a rinse, which was added rapidly. Stirring was continued for 1.5 h and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with 1 N aqueous $Na_2S_2O_3$, water and brine, dried ($MgSO_4$) and evaporated. The residue was kept under oil pump vacuum (0.3 mm Hg) for 24 h in order to remove the excess of 2-iodoethanol. Flash chromatography of the residue over silica gel (1 x 28 cm), using 1:10:90 Et_3N-EtOAc-hexane, gave **35.3** (89.7 mg, 72%) as an oil.

4-(3-Chloropropoxy)-4-methoxycyclohexa-2,5-dienone (35.5).

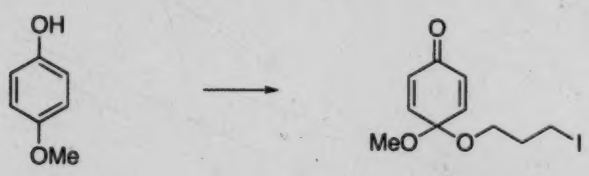


34.1 **35.5**

$PhI(OAc)_2$ (760 mg, 2.36 mmol) and K_2CO_3 (662 mg, 4.73 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, a solution of **34.1** (327 mg, 2.63 mmol) in 3-chloropropanol (2.5 mL) was injected dropwise over *ca* 1 min. Stirring was continued for 35 min and the mixture was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The residue was kept under oil pump vacuum for *ca* 12 h. Flash chromatography of the residue over silica gel, using

10% to 20% EtOAc-hexane mixtures, gave **35.5** (402 mg, 79%) as a yellow oil (in retrospect, Et_3N should be used during the chromatography): FTIR (CH_2Cl_2, cast) 2942, 2890, 1687, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.03 (quintet, J = 6.1 Hz, 2 H), 3.36 (s, 3 H), 3.65 (t, J = 6.1 Hz, 2 H), 3.73 (t, J = 6.1 Hz, 2 H), 6.18-6.32 (m, 2 H), 6.73-6.84 (m, 2 H) (strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 32.7 (t), 41.4 (t), 50.6 (q), 59.2 (t), 92.5 (s), 130.0 (d), 143.5 (d), 185.0 (s); exact mass m/z calcd for $C_{10}H_{13}{}^{35}ClO_3$ 216.05533, found 216.05520.

4-(3-Iodopropoxy)-4-methoxycyclohexa-2,5-dienone (35.6).

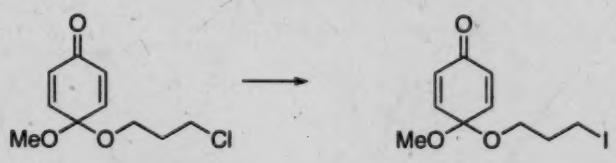


34.1 **35.6**

$PhI(OAc)_2$ (143 mg, 0.443 mmol) and K_2CO_3 (122 mg, 0.886 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, 3-iodopropanol (1 mL) was injected and, after a further 5 min, a solution of **34.1** (50.0 mg, 0.403 mmol) in 3-iodopropanol (1 mL) was added dropwise over *ca* 5 min. A further portion of 3-iodopropanol (1 mL) was used as a rinse. Stirring was continued for 50 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with 1 N aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. The residue was kept under oil pump vacuum (0.3 mm Hg) for 24 h in order to remove the excess of 3-iodopropanol. Flash chromatography of the residue over silica gel (1.8 x 24 cm), using 1:10:90 Et_3N-EtOAc-hexane, gave **35.6** (77.8 mg, 63%) as an oil: FTIR ($CHCl_3$, cast) 2939, 1689, 1675, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02-

2.12 (m, 2 H), 3.28 (t, J = 6.1 Hz, 2 H), 3.63 (t, J = 6.1 Hz, 2 H), 6.23-6.31 (m, 2 H), 6.78-6.85 (m, 2 H) (strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 2.8 (t), 33.4 (t), 50.7 (q), 62.3 (t), 92.6 (s), 130.1 (d), 143.5 (d), 185.0 (s); exact mass m/z calcd for $C_{10}H_{13}IO_3$ 307.99094, found 307.99092.

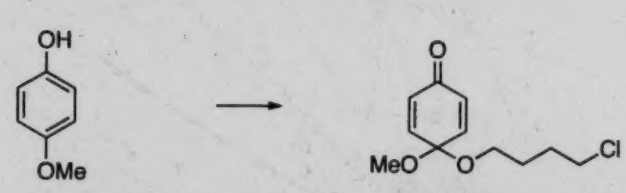
4-(3-Iodopropoxy)-4-methoxycyclohexa-2,5-dienone (35.6).



35.5 **35.6**

Acetone (2 mL, dried over K_2CO_3) was added into a mixture of **35.5** (402 mg, 1.86 mmol) and anhydrous NaI (1.116 g, 7.44 mmol). The mixture was stirred and refluxed for 20 h, cooled and partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 10% EtOAc-hexane, gave **35.6** (156 mg, 27%) as an oil, and a significant amount of a mixture of **35.5** and **35.6** was obtained. This experiment was done only once, as in the meantime I found that the product could be obtained directly from **35.1**.

4-(4-Chlorobutoxy)-4-methoxycyclohexa-2,5-dienone (35.8).



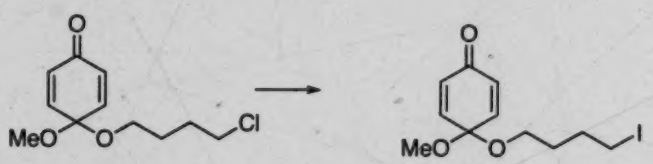
34.1 **35.8**

In this particular case the following conditions must be followed closely in order to avoid exchange of the MeO group for $OCH_2CH_2CH_2CH_2Cl$. This exchange occurs because 4-chlorobutanol decomposes to release HCl.

$PhI(OAc)_2$ (285 mg, 0.885 mmol) and K_2CO_3 (244 mg, 1.77 mmol) were placed in a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. 4-Chlorobutanol (freshly distilled, bp 70 °C, 2 mmHg, 2 mL) was added. The mixture was stirred for 5 min and a solution of **34.1** (106 mg, 0.856 mmol) in 4-chlorobutanol (1 mL) was injected dropwise over *ca* 5 min. A further portion of 4-chlorobutanol (1 mL) was used as a rinse, which was added rapidly. Stirring was continued for 3.5 h, and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The resulting thick, brown mixture was partitioned between water and Et_2O. These workup operations were done as quickly as possible since residual 4-chlorobutanol decomposes to release HCl, which catalyzes acetal exchange. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Anhydrous K_2CO_3 (200 mg) was added to the residue, which was then stored under high vacuum (0.005 mmHg) for 18 h. The residue was dissolved in Et_2O, washed with water, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.2 x 25 cm), using 1:10:90 Et_3N-EtOAc-hexane, gave **35.8** (145 mg, 74%) as an oil: FTIR ($CHCl_3$, cast) 2943, 1688, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.70-1.76 (m, 2 H), 1.82-1.89 (m, 2 H), 3.34 (s, 3 H), 3.54 (t, J = 6.5 Hz, 2 H), 3.59 (t, J = 6.3 Hz, 2H), 6.23-6.27 (m, 2 H), 6.76-6.80 (m, 2 H),

(strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.3 (t), 29.3 (t), 44.6 (t), 50.5 (q), 62.1 (t), 92.5 (s), 129.9 (d), 143.6 (d), 185.1 (s); exact mass *m/z* calcd for $C_{11}H_{15}{}^{35}ClO_3$ 230.07097, found 230.07068.

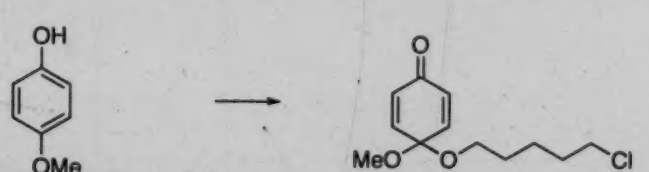
4-(4-Iodobutoxy)-4-methoxycyclohexa-2,5-dienone (35.9).



35.8 **35.9**

Acetone (5 mL, dried over K_2CO_3) was added into a stirred mixture of **35.8** (145 mg, 0.631 mmol) and anhydrous NaI (947 mg, 6.31 mmol). The mixture was stirred and refluxed for 17 h, cooled and partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with 1 N aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:10:90 Et_3N-EtOAc-hexane, gave **35.9** (190.3 mg, 94%) as an oil: FTIR (CH_2Cl_2, cast) 2940, 2833, 1686, 1638, 1503 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.66-1.72 (m, 2 H), 1.86-1.94 (m, 2 H), 3.17 (br t, *J* = 6.9, 2 H), 3.32 (s, 3 H), 3.55 (br t, *J* = 6.3 Hz, 2 H), 6.20-6.35 (m, 2 H), 6.73-6.78 (m, 2 H) (strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.2 (t), 30.0 (t), 30.8 (t), 50.5 (q), 61.7 (t), 92.4 (s), 129.8 (d), 143.5 (d), 184.9 (s); exact mass *m/z* calcd for $C_{11}H_{15}IO_3$ 322.00659, found 322.00597.

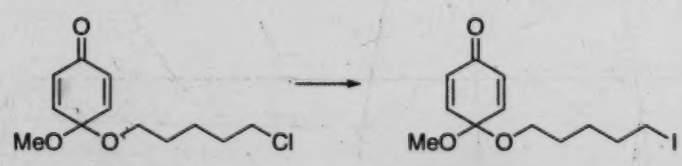
4-(5-Chloropentoxy)-4-methoxycyclohexa-2,5-dienone (35.11).



34.1 **35.11**

$PhI(OAc)_2$ (143 mg, 0.444 mmol) and K_2CO_3 (122 mg, 0.884 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 10 min, a solution of **34.1** (50.5 mg, 0.407 mmol) in freshly distilled 5-chloropentanol (1 mL) was injected dropwise over *ca* 5 min. A further portion of 5-chloropentanol (0.5 mL) was used as a rinse, which was added rapidly. Stirring was continued for 70 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water and brine, dried (Na_2SO_4) and evaporated. The residue was kept under oil pump vacuum for 9 h to remove excess of 5-chloropentanol. Flash chromatography of the residue over silica gel (1.2 x 26 cm), using 1:10:90 Et_3N-EtOAc-hexane, gave **35.11** (61.9 mg, 62%) as an oil: FTIR (CH_2Cl_2, cast) 2942, 2869, 1688, 1638 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.48-1.68 (m, 4 H), 1.75-1.85 (m, 2 H), 3.36 (s, 3 H), 3.52 (t, J = 4.8 Hz, 2 H), 3.55 (t, J = 6.2 Hz, 2 H), 6.26 (apparent d, J = 3.6 Hz, 2 H), 6.78 (apparent d, 3.6 Hz, 2 H) (strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 23.5 (t), 29.3 (t), 32.3 (t), 44.8 (t), 50.5 (q), 62.7 (t), 92.5 (s), 129.9 (d), 143.8 (d), 185.2 (s); exact mass m/z calcd for $C_{12}H_{17}{}^{35}ClO_3$ 244.08662, found 244.08647.

4-(5-Iodopentoxy)-4-methoxycyclohexa-2,5-dienone (35.12).

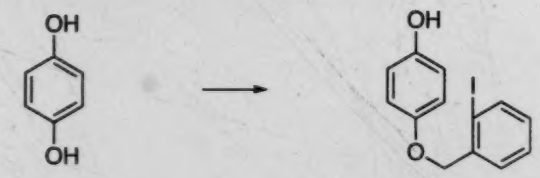


35.11 **35.12**

Acetone (5 mL, dried over K_2CO_3) was added into a mixture of **35.11** (61.9 mg, 0.254 mmol) and anhydrous NaI (381 mg, 2.54 mmol). The mixture was stirred and refluxed overnight, cooled and partitioned between water and Et_2O. The aqueous phase was

extracted with Et_2O and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 1:10:90 Et_3N-EtOAc-hexane, gave **35.12** (79.8 mg, 94%) as an oil: FTIR (CH_2Cl_2, cast) 3049, 2939, 2832, 1687, 1638, 1616 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43-1.51 (m, 2 H), 1.57-1.63 (m, 2 H), 1.83 (apparent quintet, J = 7.0 Hz, 2 H), 3.17 (t, J = 7.0 Hz, 2 H), 3.35 (s, 3 H), 3.55 (t, J = 6.4 Hz, 2 H), 6.23-6.27 (m, 2 H), 6.77-6.81 (m, 2 H) (strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 6.6 (t), 27.1 (t), 28.9 (t), 33.1 (t), 50.5 (q), 62.6 (t), 92.4 (s), 129.9 (d), 143.7 (d), 185.1 (s); exact mass m/z calcd for $C_{12}H_{17}IO_3$ 336.02225, found 336.02179.

4-(2-Iodobenzyloxy)phenol (36.2).

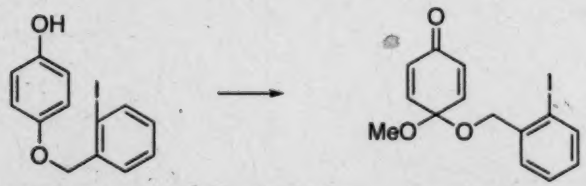


36.2

1-(Bromomethyl)-2-iodobenzene (1.047 g, 3.373 mmol) in dry DMF (4 mL plus 1 mL as a rinse) was added dropwise over 25 min into a stirred mixture of hydroquinone (1.86 g, 16.8 mmol) and K_2CO_3 (1.165 g, 8.433 mmol) in DMF (10 mL), and stirring was continued 2.25 h. The mixture was poured into water, neutralized with 10% aqueous hydrochloric acid and extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was kept under oil pump vacuum overnight. Flash chromatography of the residue over silica gel, using EtOAc-hexane mixtures from 5% EtOAc-hexane to 30% EtOAc-hexane, gave **36.2** (652.2 mg, 59%) as a solid: mp 158-160 °C; FTIR (CH_2Cl_2, cast) 3364, 1565, 1508 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.52 (s, 1 H), 5.00 (s, 2 H), 6.72-6.80 (m, 2 H), 6.82-6.91 (m, 2 H), 7.03 (t, J = 8

Hz, 1 H), 7.37 (t, J = 8 Hz, 1 H), 7.51 (d, J = 8 Hz, 1 H), 7.86 (d, J = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 74.7 (t), 97.2 (s), 116.0 (d), 116.1 (d), 128.3 (d), 128.6 (d), 129.4 (d), 139.2 (d), 139.3 (s), 149.8 (s), 152.6 (s); exact mass m/z calcd for $C_{13}H_{11}IO_2$ 325.98038, found 325.97992.

4-(2-Iodobenzyloxy)-4-methoxycyclohexa-2,5-dienone (36.3).



36.2 **36.3**

$PhI(OAc)_2$ (708.6 mg, 2.200 mmol) and K_2CO_3 (607.4 mg, 4.401 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. MeOH (10 mL) was added, and a solution of **36.2** (652.2 mg, 2.001 mmol) in MeOH (5 mL) was injected dropwise over *ca* 5 min. Further portions of MeOH (2 x 2 mL) were used as a rinse, which was added rapidly. Stirring was continued for 40 min and the black mixture was quenched by addition of saturated aqueous $NaHCO_3$. The mixture was partitioned between water and Et_2O. The combined organic extracts were washed with 1 N aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 90:10:2 hexane-EtOAc-Et_3N, gave **36.3** (622.5 mg, 87%) as an oil: FTIR (neat) 3054, 2939, 1689, 1673, 1638, 1617 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.46 (s, 3 H), 4.65 (s, 2 H), 6.26-6.34 (m, 2 H), 6.87-6.94 (m, 2 H) (strictly an AA'BB' system), 6.98 (td, J = 7.3, 2.0 Hz, 1 H), 7.33 (td, J = 7.5, 1.2 Hz, 1 H), 7.42 (br d, J = 7.5 Hz, 1 H), 7.80 (dd, J = 8, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 50.8 (q), 68.9 (t),

92.8 (s), 97.4 (s), 128.39 (d), 128.7 (d), 129.4 (d), 127.0 (d), 139.1 (d), 139.7 (s), 143.2 (d), 185.0 (s); exact mass *m/z* calcd for $C_{14}H_{13}IO_3$ 355.99094, found 355.99133.

4-(2-Chloroethoxy)-4-methoxy-4*H*-naphthalen-1-one (36.6).

36.5 **36.6**

A solution of the **36.5** in EtOAc was evaporated and the residue was kept for 10 min (and no longer) under oil pump vacuum (0.1 mmHg). When material that had been too thoroughly dried was used, the following experiment did not work and a blue color developed.

$PhI(OAc)_2$ (110 mg, 0.342 mmol) and K_2CO_3 (95.0 mg, 0.688 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, freshly distilled MeOH (10 mL) was injected and, after a further 10 min, a solution of **36.5** (69.8 mg, 0.314 mmol) in MeOH (5 mL) was added dropwise over *ca* 3 min. Stirring was continued for 25 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between water and Et_2O, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was kept under oil pump vacuum (0.3 mmHg) overnight. Flash chromatography of the residue over silica gel, using 2% Et_3N-hexane and then 1:10:40 Et_3N-EtOAc-hexane, gave **36.6** (60.7 mg, 76%) as an oil: FTIR ($CHCl_3$, cast) 2963, 1678, 1631, 1601, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.19 (s, 3 H), 3.44-3.49 (m, 1 H), 3.52-3.60 (m, 2 H), 3.66-3.71 (m, 1 H), 6.58 (dd, J = 10.5, 0.8 Hz, 1 H), 6.92 (dd, J = 10.5, 0.5 Hz, 1 H), 7.49 (apparent t, J = 7.7 Hz, 1 H), 7.65 (apparent t, J = 7.3 Hz, 1 H), 7.74

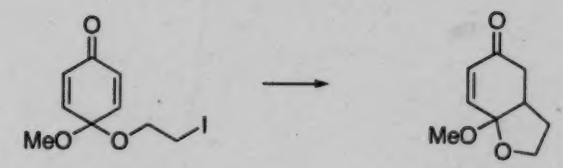
(apparent d, J = 7.9 Hz, 1 H), 8.06 (apparent d, J = 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.6 (t), 51.3 (q), 63.8 (t), 94.9 (s), 126.4 (d), 126.8 (d), 129.5 (d), 131.4 (s), 132.6 (d), 133.6 (d), 139.5 (s), 143.6 (d), 183.6 (s); exact mass m/z calcd for $C_{12}H_{10}{}^{35}ClO_2$ (M - OMe) 221.03693, found 221.03698.

4-(2-Iodoethoxy)-4-methoxy-4*H*-naphthalen-1-one (36.7).

36.6 **36.7**

DME (10 mL, dried over Na/Ph_2CO) was added into a stirred mixture of **36.6** (70.0 mg, 0.275 mmol) and anhydrous NaI (412 mg, 2.75 mmol). The mixture was stirred and refluxed for 22 h, cooled and poured into water. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with $Na_2S_2O_3$, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 1:10:90 Et_3N-EtOAc-hexane, gave **36.7** (72.8 mg, 77%) as an oil: FTIR ($CHCl_3$, cast) 2937, 1673, 1630, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.15-3.23 (m, 2 H), 3.20 (s, 1 H), 3.47 (apparent dt, J = 10.2, 6.1 Hz, 1 H), 3.69 (apparent dt, J = 9.8, 6.7 Hz, 1 H), 6.58 (d, J = 10.5 Hz, 1 h), 6.93 (d, J = 10.5 Hz, 1 H), 7.50 (apparent dt, J = 7.3, 1.3 Hz, 1 H), 7.66 (apparent dt, J = 7.3, 1.4 Hz, 1 H), 7.76 (apparent dq, J = 7.8, 0.6 Hz, 1 H), 8.06 (apparent dq, J = 7.9 Hz, 0.5); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 2.4 (t), 51.4 (q), 64.4 (t), 94.8 (s), 126.4 (d), 126.8 (d), 129.5 (d), 131.4 (s), 132.6 (d), 133.7 (d), 139.6 (s), 143.7 (d), 183.7 (s); exact mass m/z calcd for $C_{13}H_{13}IO_3$ 343.99094, found 343.99073.

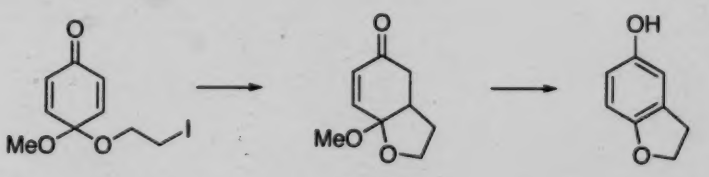
7a-Methoxy-2,3,3a,7a-tetrahydro-4*H*-benzofuran-5-one (38.2).



35.3 **38.2**

A solution of Ph_3SnH (300 mg, 0.867 mmol) and AIBN (10 mg, 0.061 mmol) in PhMe (8 mL) was added over 4 h (syringe pump) into a stirred and heated (85 °C) solution of **35.3** (170 mg, 0.578 mmol) in PhMe (37 mL). Heating was continued for 2 h after the addition. Most of the solvent was evaporated and the residual solution was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using first hexane, and then EtOAc-hexane mixtures up to 1:10 EtOAc-hexane, gave **38.2** (75 mg, 77%) as an oil: We were unable to obtain the compound pure and so the crude material was used directly for the next step.

2,3-Dihydrobenzofuran-5-ol (38.3).



35.3 **38.2** **38.3**

A solution of Ph_3SnH (0.07 mL, 0.27 mmol) and AIBN (4.8 mg, 0.030 mmol) in PhMe (5 mL) was added over 4 h (syringe pump) into a stirred and heated (85 °C) solution of **35.3** (47.8 mg, 0.163 mmol) in PhMe (10 mL). Heating was continued for 2 h after the addition, the mixture was cooled to room temperature, and $TsOH.H_2O$ (5 mg) was added. Stirring was continued for 30 min and the mixture was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica

gel, using 20% EtOAc-hexane, gave the **38.3** (17.4 mg, 79%)[78] as a white solid: mp 108-110 °C.

9b-Methoxy-2,3,3a,9b-tetrahydro-4*H*-naphtho[1,2-*b*]furan-5-one (38.5).

36.7 **38.5**

A solution of Bu_3SnH (0.08 mL, 0.3 mmol) and AIBN (10 mg, 0.061 mmol) in PhMe (5 mL) was added over 3 h (syringe pump) into a stirred and heated (95 °C) solution of **36.7** (72.8 mg, 0.212 mmol) in PhMe (15 mL). Heating was continued for 30 min after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 1:10:40 Et_3N-EtOAc-hexane, gave **38.5** (37.7 mg, 82%) as an oil [which was a single isomer (^1H NMR)]: FTIR ($CHCl_3$, cast) 2947, 2893, 1692, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.73-1.79 (m, 1 H), 2.35-2.42 (m, 1 H), 2.69 (dd, J = 16.0, 8.7 Hz, 1 H), 2.82 (dd, J = 16.0, 5.7 Hz, 1 H), 3.06-3.12 (m, 1 H), 3.20 (s, 3 H), 4.06 (dt, J = 8.3, 5.8 Hz, 1 H), 4.17 (dt, J = 8.4, 6.0 Hz, 1 H), 7.43 (t of m, J = 7.3 Hz, 1 H), 7.64 (td, J = 7.2, 1.4 Hz, 1 H), 7.70 (apparent dq, J = 7.9, 0.5 Hz, 1 H), 7.91 (apparent dq, J = 8.1, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.4 (t), 39.0 (d), 40.6 (t), 51.2 (q), 67.3 (t), 105.8 (s), 126.0 (d), 127.5 (d), 129.0 (d), 131.8 (s), 134.4 (d), 140.2 (s), 196.7 (s); exact mass *m/z* calcd for $C_{13}H_{14}O_3$ 218.09430, found 218.09453.

2,3-Dihydronaphtho[1,2-*b*]furan-5-yl Acetate (38.6).

38.5 **38.6**

Ac_2O (*ca* 1 mL) was added with stirring to **38.5** (16.0 mg, 0.0734 mmol), followed by $TsOH.H_2O$ (5 mg). A yellow color developed immediately. Stirring was continued for 3.5 h, the Ac_2O was evaporated under oil pump vacuum, and the residue was taken up in Et_2O. The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 5% EtOAc-hexane, gave the **38.6** (14.7 mg, 89%) as an oil.[79]

8a-Methoxy-3,4,4a,8a-tetrahydro-2*H*,5*H*-chromen-6-one (39.2).

35.6 **39.2**

A solution of Bu_3SnH (0.088 mL, 0.096g, 0.33 mmol) and AIBN (5 mg, 0.03 mmol) in PhMe (5 mL) was added over 5 h (syringe pump) into a stirred and heated (85 °C) solution of **35.6** (77.8 mg, 0.253 mmol) in PhMe (20 mL). Heating was continued for 1 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 2:15:85 Et_3N-EtOAc-hexane, gave **39.2** (40.2 mg, 87%) as an oil: FTIR (CH_2Cl_2, cast), 3044, 2946, 2877, 1686, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.36-1.49 (m, 2 H), 1.67-1.78 (m, 2 H), 2.04-2.11 (m, 1 H), 2.19-2.24 (m, 1 H), 2.36-2.41 (m, 1 H), 2.65-2.71 (m, 1 H), 3.37 (s, 3 H), 3.62-3.67 (m, 1 H), 3.72-3.78 (m, 1 H), 6.01 (dd, J = 10.3, 0.8 Hz, 1 H), 6.79 (d, J = 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

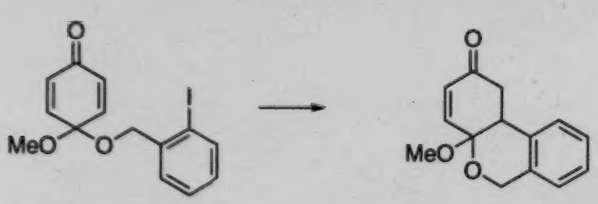
20.3 (t), 24.3 (t), 37.0 (d), 40.1 (t), 48.5 (q), 61.8 (t), 95.4 (s), 130.6 (d), 144.2 (d), 199.5 (s); exact mass *m/z* calcd for $C_{10}H_{14}O_3$ 182.09430, found 182.09428.

Chroman-6-ol (39.3).

39.2 **39.3**

TsOH.H_2O (15 mg, 0.086 mmol) was added into a stirred solution of **39.2** (40.2 mg, 0.221 mmol) in PhMe (5 mL), and stirring was continued for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel, using first hexane and then EtOAc-hexane mixtures up to 30% EtOAc-hexane, gave **39.3** (32.4 mg, 98%) as a solid: mp 97-98 °C (lit. 99-100 °C); FTIR (CH_2Cl_2, cast) 3378, 3026, 2956, 2868, 1507 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.93-2.00 (m, 2 H), 2.73 (br t, J = 6.5 Hz, 2 H), 4.12 (apparent non-binomial t, 2 H), 6.51-6.59 (m, 2 H), 6.64-6.67 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.3 (t), 24.9 (t), 66.3 (t), 114.3 (d), 115.8 (d), 117.3 (d), 123.0 (s), 148.8 (two coincident s); exact mass *m/z* calcd for $C_9H_{10}O_2$ 150.06808, found 150.06827.

4a-Methoxy-6,10b-dihydro-1*H*,4a*H*-benzo[*c*]chromen-2-one (39.5).



36.3 **39.5**

A solution of Bu_3SnH (187 mg, 0.642 mmol) and AIBN (10 mg, 0.061 mmol) in PhMe (5 mL) was added over 3 h (syringe pump) into a stirred and heated (95 °C) solution of **36.3** (191 mg, 0.535 mmol) in PhMe (15 mL). Heating was continued for 20 min after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 1:5:45 Et_3N-EtOAc-hexane, gave **39.5** (123.4 mg, 100%) as an oil, which was a single isomer (^1H NMR): FTIR ($CHCl_3$, cast) 2943, 2905, 2861, 1688, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.64-2.75 (m, 2 H), 3.29 (apparent q, J = 5.9 Hz, 1 H), 3.47 (s, 3 H), 4.83 (d, J = 15.0 Hz, 1 H), 4.89 (d, J = 15.0 Hz, 1 H) 6.12 (dd, J = 10.4, 0.9 Hz, 1 H), 6.98 (d, J = 10.4 Hz, 1 H), 7.02-7.05 (m, 1 H), 7.09-7.12 (m, 1 H), 7.19-7.24 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 41.1 (d), 44.1 (t), 49.3 (q), 63.4 (t), 95.2 (s), 123.8 (d), 126.7 (d), 127.2 (d), 127.9 (d), 130.7 (d), 131.8 (s), 133.8 (s), 142.6 (d), 197.9 (s); exact mass m/z calcd for $C_{14}H_{14}O_3$ 230.09430, found 230.09417.

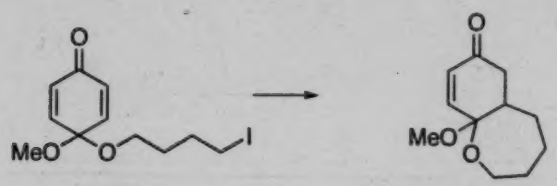
6*H*-Benzo[*c*]chromen-2-ol (39.6).

39.5 **39.6**

TsOH.H_2O (15 mg) was added into a stirred solution of **39.5** (37.4 mg, 0.164 mmol) in a mixture of acetone (2 mL) and CH_2Cl_2 (1 mL), and stirring was continued for 5 min. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried and evaporated. Flash chromatography of the residue over silica gel, using 1:9 EtOAc-hexane, gave **39.6** (28.9 mg, 90%) as an oil: FTIR (CH_2Cl_2, cast) 3382, 1496, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.58-4.64 (br s, 1 H), 5.06 (s, 3 H), 6.71 (dd, J = 8.7, 2.9 Hz, 1 H), 6.87 (d, J = 8.6 Hz, 1H), 7.14 (br d, J = 7.5 Hz, 1 H),

7.19 (d, J = 2.9 Hz, 1 H), 7.28 (td, J = 7.4, 1.2 Hz, 1 H), 7.36 (td, J = 7.4, 1.3 Hz, 1 H), 7.60 (d, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 68.5 (t), 109.7 (d), 116.3 (d), 118.1 (d), 122.0 (d), 123.8 (s), 124.6 (d), 127.8 (d), 128.4 (d), 129.9 (s), 131.8 (s) 148.8 (s) 150.5 (s); exact mass m/z calcd for $C_{13}H_{10}O_2$ 198.06808, found 198.06769.

9a-Methoxy-2,3,4,5,5a,9a-hexahydro-6*H*-benzo[*b*]oxepin-7-one (40.2).



40.2 **35.9**

A solution of Bu_3SnH (0.12 mL, 120 mg, 0.42 mmol) and AIBN (10 mg, 0.061 mmol) in PhMe (5 mL) was added over 3 h (syringe pump) into a stirred and heated (95 °C) solution of **35.9** (114.1 mg, 0.3543 mmol) in PhMe (15 mL). Heating was continued for 2 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 1:10:90 Et_3N-EtOAc-hexane, gave **40.2** (53.3 mg, 77%) as an oil [which was a single isomer (^{1}H NMR)]: FTIR (CH_2Cl_2, cast) 2930, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.44 (m, 2 H), 1.54-1.70 (m, 3 H), 1.80-1.88 (m, 1 H), 2.29 (apparent dq, J = 16.2, 1.4 Hz, 1 H), 2.40-2.45 (m, 1 H), 2.90 (dd, J = 16.2, 5.5 Hz, 1 H), 3.29 (s, 3 H), 3.64 (apparent d of sextets, J = 12.6, 1.8 Hz, 1 H), 3.78-3.86 (m, 1 H), 5.96 (dd, J = 10.4, 1.4 Hz, 1 H), 6.61 (dd, J = 10.4, 2.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.8 (t), 29.8 (t), 29.9 (t), 43.6 (t), 46.7 (d), 49.5 (q), 61.6 (t), 99.6 (s), 128.9 (d), 146.4 (d), 198.9 (s); exact mass m/z calcd for $C_{11}H_{16}O_3$ 196.10994, found 196.11050.

2,3,4,5-Tetrahydrobenzo[b]oxepin-7-ol (40.3).

40.2 **40.3**

$TsOH.H_2O$ (10 mg) was added into a stirred solution of **40.2** (47.7 mg, 0.243 mmol) in a mixture of CH_2Cl_2 (2 mL) and acetone (0.1 mL), and stirring was continued for 40 min. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 1:4 EtOAc-hexane, gave **40.3** (38.3 mg, 96%) as a solid: mp 81-83 °C (lit. 83-84 °C).

4a-Methoxy-1,2,6,10b-tetrahydro-4a*H*-benzo[*c*]chromen-2-ol (41.2).

39.5 **41.2**

$CeCl_3.7H_2O$ (76.7 mg, 0.206 mmol) and then $NaBH_4$ (23.4 mg, 0.618 mmol) were added into a stirred and cooled (-78 °C) solution of **39.5** (47.7 mg, 0.206 mmol) in dry MeOH (5 mL). After the addition the cooling bath was removed and stirring was continued for 55 min. Water was added and the mixture was extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 1:15:35 Et_3N-EtOAc-hexane, gave **41.2** (35.9 mg, 75%) as an oil [which was a single isomer (^1H NMR)]: FTIR (CH_2Cl_2, cast) 3378, 2942, 2858, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.76 (dt, J = 10.5, 13.3 Hz, 1 H), 2.17-2.23 (m, 1 H), 2.82 (dd, J = 13.5, 3.0 Hz, 1 H), 3.38 (s, 3 H), 4.41 (q, J = 4.9 Hz, 1 H), 4.75 (AB q, J = 15.0 Hz, $\Delta\nu_{AB}$ = 13.2 Hz, 2 H), 6.01 (apparent AB q, J = 10.5 Hz, $\Delta\nu_{AB}$ = 7.8 Hz, 2 H), 6.98 (d, J = 7.2 Hz, 1 H), 7.13-7.22 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.4 (d),

41.2 (t), 49.1 (q), 62.8 (t), 67.86 (d), 67.87 (d), 95.8 (s), 123.5 (d), 125.2 (d), 126.2 (d), 126.8 (d), 128.8 (d), 132.2 (s), 135.0 (s), 136.5 (d); exact mass *m/z* calcd for $C_{14}H_{16}O_3$ 232.10994, found 232.11016.

6*H*-Benzo[*c*]chromene (41.3).

41.2 **41.3**

$TsOH.H_2O$ (35.1 mg, 0.201 mmol) was added into a stirred solution of **41.2** (35.9 mg, 0.155 mmol) in a mixture of $CHCl_3$ (10 mL) and acetone (1 mL), and stirring was continued overnight [TLC control (silica, hexane or 5% EtOAc-hexane) suggested the reaction was over within 4 min]. The mixture was evaporated and the residue was partitioned between hexane and water. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 5% CH_2Cl_2-hexane, gave **41.3** (23.7 mg, 85%) as an oil.

8a-Methoxy-6-phenyl-3,4,4a,5,6,8a-hexahydro-2*H*-chromen-6-ol (41.8).

39.2 **41.8**

PhMgBr (0.60 mL, 0.60 mmol, 1 M in THF) was added at a fast dropwise rate into a stirred solution of **39.2** (55.0 mg, 0.302 mmol) in THF (5 mL). Stirring was continued

for 2 h and the mixture was then cooled to 0 °C and quenched with water. The solvent was evaporated and the residue was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20:30 Et_3N-EtOAc-hexane, gave **41.8** (59.5 mg, 75%) as a colorless solid: mp 131-133 °C; FTIR (CH_2Cl_2 cast) 3406, 3033, 2862, 1490, 1274, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22-1.32 (m, 2 H), 1.68-1.81 (m, 3 H), 1.96-2.06 (m, 1 H), 2.19 (s, 1 H), 2.44 (t, J = 13.2 Hz, 1 H), 3.36 (s, 3 H), 3.60-3.68 (m, 2 H), 5.85 (dd, J = 5.2, 2 Hz, 1 H), 6.07 (d, J = 5.2, 1 H), 7.23-7.27 (m, 3 H), 7.47 (d, J = 7.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.18 (t), 24.36 (t), 33.53 (d), 42.49 (t), 48.02 (q), 61.45 (t), 74.76 (s), 95.99 (s), 125.99 (d), 126.75 (d), 127.42 (d), 128.15 (d), 135.63 (d), 144.56 (s); exact mass m/z calcd for $C_{16}H_{20}O_3$ 260.14124, found 260.14086.

6-Phenylchroman (41.9).

41.8 **41.9**

$TsOH.H_2O$ (10 mg) was added into a stirred solution of **41.8** (47.8 mg, 0.184 mmol) in CH_2Cl_2 (10 mL), and stirring was continued for 1 h. The mixture was then partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:4 CH_2Cl_2-hexane, gave **41.9** (30.5 mg, 79%) as a colorless solid: mp 43-44 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.01-2.06 (m, 2 H), 2.85 (t, J = 6.8 Hz, 2 H), 4.22 (t, J = 5.2 Hz, 2 H), 6.86 (d, J = 8.2 Hz, 1 H),

7.26-7.34 (m, 3 H), 7.38-7.42 (m, 2 H), 7.52-7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.41 (t), 25.04 (t), 66.57 (t), 117.04 (d), 122.37 (s), 125.99 (d), 126.49 (d), 126.66 (d), 128.44 (d), 128.63 (d), 133.25 (s), 141.01 (s), 154.55 (s); exact mass *m/z* calcd for $C_{15}H_{14}O$ 210.10446, found 210.10445.

1-Allyl-4a-methoxy-6,10b-dihydro-1*H*,4a*H*-benzo[*c*]chromen-2-one (41.12).

38.3 **41.12**

AIBN (10 mg, 0.061 mmol) and allyltributyltin (170 mg, 0.512 mmol) were added into a stirred solution of **38.3** (83.5 mg, 0.256 mmol) in PhMe (5 mL), and the mixture was then refluxed for 34 h, cooled and evaporated. Flash chromatography of the residue over silica gel, using 1:5:45 Et_3N-EtOAc-hexane, gave a solid, which appeared to be a mixture of isomers corresponding to the desired product **41.12** (^1H NMR). TLC analysis (silica, 30% EtOAc-hexane), showed two close spots. The crude material was used directly for the next step.

1-Allyl-6*H*-benzo[*c*]chromen-2-ol (41.13).

41.12 **41.13**

$TsOH.H_2O$ (20 mg, 0.11 mmol) was added into a stirred solution of **41.12** (mixture of isomers) in CH_2Cl_2 (4 mL). After 45 min, acetone (10 mL) was added and stirring was continued overnight, since it was not clear from TLC examination (silica, 30% EtOAc-hexane) of the mixture if the reaction was over. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 20% EtOAc-hexane, gave **41.13** (44.1 mg, 72%) as an oil: FTIR (CH_2Cl_2, cast) 3418, 3076, 2976, 2835, 1635, 1571 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.71 (apparent dt, J = 2.3, 2.1 Hz, 2 H), 4.81-4.85 (br m, 1 H), 4.89 (s, 2 H), 5.24 (dq, J = 17.3, 1.6 Hz, 1 H), 5.35 (dq, J = 10.3, 1.8 Hz, 1 H), 6.25-6.34 (m, 1 H), 6.80 (d, J = 8.6 Hz, 1 H), 6.89 (d, J = 8.6 Hz, 1 H), 7.23 (br d, J = 6.4 Hz, 1 H), 7.28 (td, J = 7.3, 1.1 Hz, 1 H), 7.33 (td, J = 7.5, 1.4 Hz, 1 H), 7.62 (d, J = 7.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 33.0 (t), 69.3 (t), 116.2 (d), 116.6 (d), 117.2 (t), 121.3 (s), 124.8 (s), 124.9 (d), 126.0 (d), 127.2 (d), 127.9 (d), 130.3 (s), 134.0 (s), 135.6 (d), 150.0 (s), 150.5 (s); exact mass *m/z* calcd for $C_{16}H_{14}O_2$ 238.09938, found 238.09982.

5-(Allyloxy)-1,4-naphthoquinone (45.2).

41.2 **45.2**

Allyl bromide (1.30 g, 15.0 mmol) and silver(I) oxide (2.61 g, 11.3 mmol) were added into a stirred solution of juglone (**45.1**) (1.31 g, 7.52 mmol) in CH_2Cl_2 (20 mL), and stirring was continued for 20 h. Additional portions of allyl bromide (0.60 mL, 6.9 mmol) and silver(I) oxide were added, and the mixture was then refluxed for 11 h. The mixture was cooled and partitioned between water and CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous

$NaHCO_3$ and water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (25 x 2.8 cm), using 1:4 EtOAc-hexane, gave **45.2** (1.28 g, 79%) as a yellow-orange solid: mp 54-56 °C; FTIR ($CHCl_3$, cast) 1659, 1613, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 400.1 MHz) δ 4.66 (dt, J = 4.8, 1.7 Hz, 2 H), 5.31 (dq, J = 10.7, 1.6 Hz, 1 H), 5.60 (dq, J = 17.4, 1.6 Hz, 1 H), 6.03 (apparent q of t, J = 10.7, 4.7 Hz, 1 H), 6.80 (AB q, J = 2.0, 10.2 Hz, $\Delta\nu_{AB}$ = 6.3 Hz, 2 H), 7.22 (dd, J = 8.2, 1.3 Hz, 1 H), 7.58 (t, J = 8.2 Hz, 1 H), 7.65 (dd, J = 6.3, 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 69.7 (t), 117.9 (t), 119.2 (d), 119.3 (d), 120.0 (s), 131.9 (d), 134.0 (s), 134.7 (d), 136.0 (d), 140.8 (d), 158.5 (s) 184.0 (s) 185.1 (s); exact mass m/z calcd for $C_{13}H_{10}O_3$ 214.06299, found 214.06276.

5-(Allyloxy)naphthalene-1,4-diol (45.3).

45.2 **45.3**

A solution of $Na_2S_2O_4$ (1.92 g, 11.0 mmol) in water (10 mL) was added into a solution of **45.2** (0.7871 g, 3.678 mmol) in Et_2O (50 mL), and the mixture was stirred for 40 min. Water (20 mL) was added and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated to give **45.3** (0.7926 g, 100%) as beige flakes: mp 133-134 °C; FTIR ($CHCl_3$, cast) 3400, 3196, 2938, 1636, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.76 (dt, J = 4.9, 1.3 Hz, 2 H), 4.89 (s, 1 H), 5.40 (dq, J = 10.4, 1.0 Hz, 1 H), 5.49 (dq, J = 17.2, 1.3 Hz, 1 H), 6.09-6.18 (m, 1 H), 6.72 (AB q, J = 8.2 Hz, $\Delta\nu_{AB}$ = 19.9 Hz, 2 H), 6.82 (d, J = 7.7 Hz, 1 H), 7.31 (t, J = 7.9 Hz, 1 H), 7.74 (dd, J = 8.6, 0.9 Hz, 1 H), 9.03 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 70.3 (t), 106.3 (d), 109.4 (d), 110.9 (d), 115.8 (s), 115.9 (d), 119.8 (t), 125.2

(d), 126.9 (s), 131.8 (d), 143.7 (s) 148.4 (s) 155.1 (s); exact mass *m/z* calcd for $C_{13}H_{12}O_3$ 216,07864, found 216.07872.

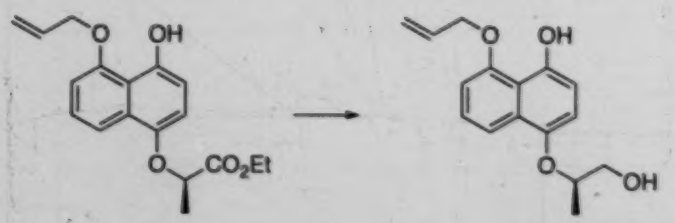
Ethyl (2*R*)-2-[[5-(Allyloxy)-4-hydroxynaphthalen-1-yl]oxy]propionate (45.4).

45.3 **45.4**

A solution of ethyl (*S*)-2-[(trifluoromethanesulfonyl)oxy]propionate (3.50 g, 14.0 mmol) in CH_2Cl_2 (10 mL) was added over 10 min into a stirred and cooled (-78 °C) mixture of **45.3** (0.6117 g, 3.045 mmol) and Cs_2CO_3 (0.9945 g, 3.045 mmol) in CH_2Cl_2 (15 mL). Stirring at -78 °C was continued arbitrarily for 18 h. The progress of the reaction was monitored by TLC (silica, 1:3 EtOAc-hexane); no further change seemed to occur after *ca* 3 h. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (23 x 2.4 cm), using 1:10 to 1:5 EtOAc-hexane mixtures, gave **45.4** [0.4789 g, 50% or 88% after correction for recovered **45.3** (0.2448 g, 40%) as a clear, colorless oil: FTIR ($CHCl_3$, cast) 3415, 2984, 1750, 1632, 1609, 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.2 Hz, 3 H), 1.68 (d, *J* = 6.8 Hz, 3 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.75 (dt, *J* = 5.6, 1.8 Hz, 2 H), 4.78 (q, *J* = 6.8 Hz, 1 H), 5.39 (dq, *J* = 10.4, 1.2 Hz, 1 H), 5.48 (dq, *J* = 17.2, 1.5 Hz, 1 H), 6.08-6.18 (m, 1 H), 6.7 (s, 2 H), 6.83 (dd, *J* = 7.8, 0.7 Hz, 1 H), 7.31 (dd, *J* = 7.8, 8.5 Hz, 1 H), 7.92 (dd, *J* = 8.6, 1.0 Hz, 1 H), 9.04 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.2 (q), 18.7 (q), 61.2 (t), 70.4 (t), 74.1 (s), 106.4 (d),

108.9 (d), 109.5 (d), 115.9 (s), 116.7 (d), 119.8 (t) 125.3 (d) 128.6 (s), 131.8 (d), 146.2 (s), 149.0 (s), 154.9 (s), 172.5 (s); exact mass *m/z* calcd for $C_{18}H_{20}O_4$ 316.13107, found 316.13089.

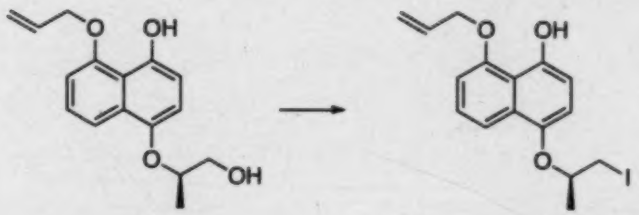
8-Allyloxy-4-[(1*R*)-2-hydroxy-1-methylethoxy]naphthalen-1-ol (45.5).



45.4 **45.5**

$LiAlH_4$ (0.0149 g, 0.392 mmol) was added into a stirred solution of **45.4** (0.1661 g, 0.5223 mmol) in THF (15 mL). After 10 min, aqueous sodium potassium tartrate (20% w/v, 5 mL) was added. The mixture was stirred for a further 20 min, and then partitioned between water and Et_2O. The aqueous phase was extracted twice with Et_2O and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (21 x 2.3 cm), using 1:1 EtOAc-hexane, gave **45.5** (0.1469, 100%) as clear, light green flakes: mp 76-78 °C; FTIR ($CHCl_3$, cast) 3414, 2975, 2932, 1630, 1609, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 400.1 MHz) δ 1.30 (d, J = 6.5, 3 H), 3.78-3.85 (m, 2 H), 4.50-4.59 (m, 1 H), 4.77 (dt, J = 5.6, 1.4 Hz, 2 H), 5.41 (dq, J = 10.3, 1.2 Hz, 1 H), 5.50 (dq, J = 17.3, 1.2 Hz, 1 H), 6.10-6.20 (m, 1 H), 6.83 (br d, J = 7.5, 1 H), 6.84 (AB q, J = 8.6 Hz, $\Delta\nu_{AB}$ = 148.2 Hz, 2 H), 7.30 (AB q, J = 7.8 Hz, $\Delta\nu_{AB}$ = 3.6 Hz, 1 H), 7.84 (dd, J = 8.5, 0.9 Hz, 1 H), 9.06 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 16.2 (q), 66.6 (t), 70.4 (t), 76.6 (d), 106.2 (d), 109.3 (d), 111.3 (d), 115.8 (s), 116.1 (d), 119.7 (t), 125.2 (d) 129.3 (s) 131.7 (d), 145.7 (s), 148.7 (s), 155.0 (s); exact mass *m/z* calcd for $C_{16}H_{18}O_4$ 274.12051, found 274.12067.

8-Allyloxy-4-[(1*R*)-2-iodo-1-methylethoxy]naphthalen-1-ol (45.6).



45.5 **45.6**

Ph_3P (0.3337 g, 1.272 mmol), and then imidazole (0.0914 g, 1.34 mmol), were added into a stirred solution of **45.5** (0.1255 g, 0.4547 mmol) in THF (10 mL) (Ar atmosphere). The mixture was transferred to an ice bath (continued stirring), and I_2 (0.2620 g, 1.032 mmol) was added in one portion. After 2.5 h, the ice bath was removed and stirring was continued overnight. The mixture was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with aqueous $Na_2S_2O_3$ (10% w/v), water, and dilute hydrochloric acid (5%), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (24 x 2.8 cm), using 0-15% EtOAc-hexane mixtures, gave **45.6** (0.1568 g, 89%) as an oil: FTIR ($CHCl_3$, cast) 3414, 2977, 2930, 1631, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (d, J = 6.0, 3 H), 3.35-3.47 (m, 2 H), 4.32-4.42 (m, 1 H), 4.76 (dt, J = 5.6, 1.3 Hz, 2 H), 5.40 (dq, J = 10.5, 1.2 Hz, 1 H), 5.49 (dq, J = 17.2, 1.2 Hz, 1 H), 6.07-6.21 (m, 1 H), 6.72-6.84 (m, 3 H), 7.30 (AB q, J = 7.8 Hz, $\Delta\nu_{AB}$ = 3.6 Hz, 1 H), 7.86 (dd, J = 8.6, 0.9, 1 H), 9.06 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.4 (t), 20.3 (q), 70.3 (t), 74.6 (d), 106.3 (d), 109.2 (d), 111.1 (d), 115.9 (s), 116.5 (d), 119.7 (t), 125.3 (d), 129.3 (s), 131.7 (d), 145.3 (s), 148.9 (s), 154.9 (s); exact mass m/z calcd for $C_{16}H_{17}IO_3$ 384.02225, found 384.02247.

8-Allyloxy-4-[(1*R*)-2-iodo-1-methylethoxy]-4-methoxy-4*H*-naphthalen-1-one (47.2).

45.6 **47.2**

DDQ (0.0878 g, 0.388 mmol), followed immediately by K_2CO_3 (0.0534 g, 0.387 mmol), was added into a stirred solution of **45.6** (0.0995 g, 0.258 mmol) in MeOH. After 4 min, aqueous $Na_2S_2O_3$ (2 mL, 10% w/v) and water (10 mL) were added. The mixture was partitioned between EtOAc and water, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (21 x 2 cm), using 1:4 EtOAc-hexane, gave **47.2** (0.0938 g, 87%) as an oil [*ca* 1:1.15 mixture of diastereoisomers (^{1}H NMR)]: FTIR ($CHCl_3$, cast) 3396, 2924, 1659, 1608, 1582 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, signals for both isomers reported, as extensive overlapping prevents allocation of signals to individual isomers) δ 1.23 (d, *J* = 6.2, 1.4 H), 1.35 (d, *J* = 6.1 Hz, 1.6 H), 2.90 (dd, *J* = 10.0, 7.3 Hz, 1.6 H), 3.01 (dd, *J* = 10.0, 3.8 Hz, 1.4 H), 3.10 (s, 1.6 H), 3.13 (s, 1.4 H), 3.20-3.33 (m, 1 H), 3.72-3.86 (m, 1 H), 4.66-4.70 (m, 2 H), 5.35 (apparent dt, *J* = 10.7, 1.5 Hz, 1 H), 5.68 (apparent dq, *J* = 17.2, 1.7 Hz, 1 H), 6.04-6.17 (m, 1 H), 6.47 (apparent dd, *J* = 10.4, 1.5 Hz, 1 H), 6.75 (d, *J* = 10.5 Hz, 0.5 H), 6.81 (d, *J* = 10.5 Hz, 0.5 H), 7.01 (dd, *J* = 8.3, 2.8 Hz, 1 H), 7.42 (dd., *J* = 7.8, 2.9, 1.0 Hz, 1 H), 7.58 (td, *J* = 8.1, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.6 (t), 13.084 (t), 21.6 (q), 22.4 (q) 51.3 (q), 51.4 (q), 68.9 (d), 69.3 (d), 69.6 (two coincident t), 95.3 (s), 95.4 (s), 114.1 (d), 114.2 (d), 117.6 (t), 117.7 (t), 119.7 (d), 119.8 (d), 120.5 (s), 120.6 (s), 132.25 (d), 132.28 (d), 133.9 (d), 134.0 (d), 134.4 (d), 139.9 (d), 140.5 (d), 143.0 (s), 143.2 (s), 158.7 (s), 158.8 (s), 183.14 (s), 183.15 (s); exact mass *m/z* calcd for $C_{17}H_{19}IO_4$ 414.03281, found 414.03241.

(2*R*)-6-Allyloxy-9b-methoxy-2-methyl-2,3,3a,9b-tetrahydro-4*H*-naphtho[1,2-*b*]furan-5-one (47.3).

47.2 **47.3**

A solution of Bu_3SnH (0.19 mL, 0.70 mmol) and AIBN (0.010 g) in PhMe (5 mL) was added over 9 h (syringe pump) into a stirred and heated (85 °C) solution of **47.2** (0.2246 g, 0.5399 mmol) in PhMe (10 mL). Heating at 85 °C was continued for 6 h after the addition. The solvent was evaporated, and flash chromatography of the residue over silica gel (26 x 2.8 cm), using 1:20:30 Et_3N-EtOAc-hexane, gave **47.3** (0.1286 g, 82%) as an oil: FTIR ($CHCl_3$, cast) 2968, 2934, 1694, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, signals for both isomers reported, as extensive overlapping prevents allocation of signals to individual isomers) δ 1.26 (d, J = 6.2 Hz, 1.5 H), 1.40 (d, J = 6.2 Hz, 1.5 H), 1.87-1.96 (m, 0.5 H), 2.01-2.12 (m, 0.5 H), 2.39-2.49 (m, 0.5 H), 2.62-2.86 (m, 2 H), 3.00-3.14 (m, 1 H), 3.13 (s, 1.5 H), 3.15 (s, 1.5 H), 4.34-4.51 (m, 1 H), 4.54-4.69 (m, 2 H), 5.31 (apparent dt, J = 10.6, 1.5 Hz, 1 H), 5.56 (dm, J = 17.2 Hz, 1 H), 5.99-6.12 (m, 1 H), 6.94 (br d, J = 8.3 Hz, 1 H), 7.32 (apparent d of quintets, J = 8.6, 0.9 Hz, 1 H), 7.52 (apparent sextet, J = 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz, signals for both isomers reported, as extensive overlapping prevents allocation of signals to individual isomers) δ 21.4 (q), 22.6 (q), 37.7 (t), 39.4 (t), 39.9 (d), 40.8 (d), 43.4 (t), 44.5 (t), 50.4 (q), 51.3 (q), 69.47 (t) 69.48 (t) 75.2 (d), 75.4 (d), 105.6 (s), 106.6 (s), 113.2 (d), 113.4 (d), 117.5 (two coincident t), 119.5 (d), 119.7 (d), 122.3 (s), 122.4 (s), 132.40 (d), 132.44 (d), 134.1 (d), 134.5 (d), 142.6 (s), 142.8 (s), 156.4 (s), 156.9 (s), 196.2 (s), 196.4 (s); exact mass m/z calcd for $C_{17}H_{20}O_4$ 288.13617, found 288.13558.

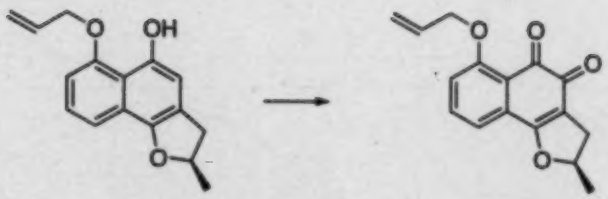
(2*R*)-6-Allyloxy-2-methyl-2,3-dihydronaphtho[1,2-*b*]furan-5-ol (47.*A*).

47.3 **47.*A***

AcOH (*ca* 0.3 mL) was added into a stirred solution of **47.3** (0.0733 g, 0.253 mmol) in $CHCl_3$ (5 mL), and stirring was continued for 2 h. Evaporation of the solvent at room temperature (oil pump vacuum) and flash chromatography of the residue over silica gel (22 x 2.8 cm), using 1:10 EtOAc-hexane, gave **47.*A*** (57.6 mg, 88%) as a white solid: mp 77-78 °C; FTIR ($CHCl_3$, cast) 3423, 2972, 2928, 1641, 1605, 1524 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50 (d, *J* = 6.3 Hz, 3 H), 2.92 (apparent dd, *J* = 16.0, 7.6 Hz, 1 H), 3.41 (apparent dd, *J* = 15.4, 8.9 Hz, 1 H) (formally part of an ABX system), 4.74 (apparent d, *J* = 5.6 Hz, 2 H), 4.99-5.06 (m, 1 H), 5.38 (dq, *J* = 10.5, 1.1 Hz, 1 H), 5.48 (dq, *J* = 17.3, 1.4 Hz, 1 H), 6.13 (ddt, *J* = 17.3, 10.5, 5.6 Hz, 1 H), 6.71 (d, *J* = 7.6 Hz, 1 H), 6.73 (s, 1 H), 7.23 (t, *J* = 8.2 Hz, 1 H), 7.48 (dd, *J* = 8.4, 0.8 Hz, 1 H), 9.00 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.9 (q), 38.4 (t), 70.2 (t), 79.6 (d), 105.1 (d), 107.1 (d), 114.2 (s), 115.6 (d), 119.6 (t), 121.6 (s), 121.9 (s) 125.1 (d) 131.8 (d), 147.5 (s), 148.3 (s), 155.2 (s); exact mass *m/z* calcd for $C_{16}H_{16}O_3$ 256.10995, found 256.10936.

In another experiment, an NMR sample (43.2 mg, 0.149 mmol) was left overnight in $CDCl_3$, and evaporation of the solvent, followed by flash chromatography, gave **47.*A*** (37.1 mg, 97%).

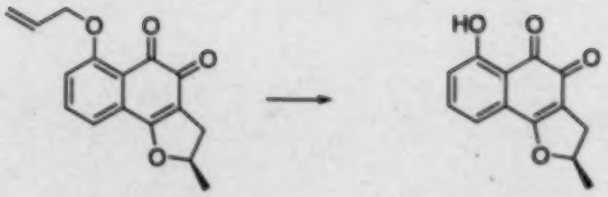
(2*R*)-6-Allyloxy-2-methyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (47.*5*).



47.4 **47.5**

$[PhSe(O)]_2O$ (70%, 0.1859 g, 0.5162 mmol) was added in one portion into a stirred solution of **47.4** (0.0666 g, 0.258 mmol) in THF (10 mL). After 12 min, water (20 mL) was added and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (22 x 2.2 cm), using 3:7 to 1:1 EtOAc-hexane mixtures, gave **47.5** (0.0676 g, 96%) as a red powder. Recrystallization from $CHCl_3$-hexane (dissolution in $CHCl_3$ and addition of hexane) gave **47.5** (0.574 g, 82%) as orange-red needles: mp 118-120 °C; FTIR ($CHCl_3$, cast) 2978, 1683, 1647, 1621, 1576 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54 (d, J = 6.4, 3 H), 2.70 (apparent dd, J = 15.3, 7.3 Hz, 1 H), 3.24 (apparent dd, J = 15.3, 9.8 Hz, 1 H) (formally part of an ABX system), 4.68 (dt, J = 4.4, 1.8 Hz, 2 H), 5.15-5.24 (m, 1 H), 5.34 (dq, J = 10.7, 1.6 Hz, 1 H), 5.74 (dq, J = 17.2, 1.7 Hz, 1 H), 5.99-6.08 (m, 1 H), 7.11 (d, J = 8.6 Hz, 1 H), 7.26 (dd, 7.4, 0.8 Hz, 1 H), 7.53 (dd, 8.6, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (q), 33.5 (t), 69.4 (t), 84.0 (d), 114.5 (s), 117.4 (d), 117.7 (t), 117.9 (d), 118.3 (s), 129.5 (s), 131.5 (d) 135.5 (d) 160.7 (s), 169.2 (s), 175.5 (s), 180.0 (s); exact mass m/z calcd for $C_{16}H_{16}O_4$ 272.10486, found 272.10419.

(2*R*)-6-Hydroxy-2-methyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione [*ent*-nocardione A] (47.6).



47.5 **47.6**

Dimedone (0.0623 g, 0.444 mmol) and then $Pd(PPh_3)_4$ (0.0259 g, 0.0223 mmol) were added into a stirred solution of **47.5** (0.0574 g, 0.211 mmol). Stirring was continued for 4 min, and the mixture was then evaporated (rotary evaporator) at room temperature. Flash chromatography of the reside over silica gel (24 x 1.8 cm), using 0.1:10:90 HCO_2H-EtOAc-$CHCl_3$, gave a crude red powder (0.0557 g). (Use of acid in the solvent for chromatography is essential for effective purification, but recrystallization is still necessary.) Recrystallization from EtOAc-hexane gave **47.6** [(*R*)-(+)-nocardione A, *ent*-nocardione A] (0.0359 g, 74%) in the form of curled red needles: mp 168-169 °C, [if the crystalline material is dissolved in a solvent and the solution evaporated to leave a powder, the powder changes to needles (mp 168-169 °C) at or below 158 °C]; $[\alpha]_D^{25}$ +36.8, *c* = 1.0 $CHCl_3$, 10 cm cell; $[\alpha]_D^{25}$ +49.5, *c* = 0.97 $CHCl_3$, 1 cm cell, Lit.[44] $[\alpha]_D^{21}$ -56.0, *c* = 0.97 $CHCl_3$, Lit.[45] $[\alpha]_D^{26}$ -85.4, *c* = 1.0 $CHCl_3$; FTIR ($CHCl_3$, cast) 2961, 2925, 1643, 1615, 1589, 1499 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56 (d, *J* = 6.3, 3 H), 2.72 (apparent dd, *J* = 15.4, 7.2 Hz, 1 H), 3.25 (apparent dd, *J* = 15.3, 9.8 Hz, 1 H) (formally part of an ABX system), 5.19-5.27 (m, 1 H), 7.11 (dd, *J* = 8.7, 0.9 Hz, 1 H), 7.18 (br d, *J* = 6.7 Hz, 1 H), 7.53 (dd, *J* = 8.6, 7.3 Hz, 1 H), 11.93 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (q), 33.4 (t), 84.5 (d), 113.4 (s), 115.1 (s), 117.4 (d), 123.2 (d), 127.4 (s), 137.5 (d), 164.4 (s), 169.1 (s) 175.0 (s) 185.4 (s); exact mass *m/z* calcd for $C_{13}H_{10}O_4$ 230.05791, found 230.05774.

HPLC conditions for measurement of ee: column, Chiracell AD-RHCD-CC012 column (0.46 cm x 15 cm); eluant 2:1 water-MeCN; flow rate 0.6 mL/min; detection at 230 nm, temperature 25 °C; sample concentration and injection value 1 mL/mg in MeCN x 0.5 μL. Under these conditions (*S*)-(-)-nocardione A was detected at R_t 40.31 min, and (*R*)-

(+)-nocardione A was detected at R_t 42.82 min. Our synthetic (*R*)-nocardione A had 98.55% ee.

2-[(4-Methoxymethoxy)phenylamino]ethanol (54.2).

54.1 **54.2**

Ethanolamine (1.13 mL, 18 mmol) was injected into an oven-dried round-bottomed flask containing **54.1** (990.0 mg, 3.75 mmol) (Ar atmosphere). Oven-dried K_2CO_3 (2.58 g, 18 mmol), CuI (178 mg, 0.94 mmol) and L-proline (215 mg, 1.87 mmol) were tipped in. The mixture was suspended in dry DMSO (5 mL) and the flask was lowered into an oil bath preset at 85 °C. The mixture was stirred for 45 min, cooled to room temperature and partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with water (twice) and brine, and dried ($MgSO_4$). Flash chromatography of the residue over silica gel (2.6 x 18 cm), using EtOAc-hexane mixtures from 0% to 100% EtOAc, gave **54.2** (609 mg, 82%): FTIR ($CHCl_3$, cast) 3381, 2944, 1512, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.27 (t, *J* = 5.5 Hz, 2 H), 3.48 (s, 3 H), 3.82 (t, *J* = 5.0 Hz, 2 H), 5.08 (s, 2 H), 6.62 (apparent d, *J* = 8.9 Hz, 2 H), 6.93 (apparent d, *J* = 8.9 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 47.0 (t), 55.8 (q), 61.3 (t), 95.6 (t), 114.5 (d), 118.0 (d), 143.4 (s), 149.9 (s); exact mass *m/z* calcd for $C_{10}H_{15}NO_3$ 197.10519, found 197.10390.

(2-Iodoethyl)[4-(methoxymethoxy)phenyl]amine (54.3).

54.2 **54.3**

Imidazole (403 mg, 5.93 mmol), Ph_3P (1.61 g, 6.16 mmol), and I_2 (1.16 g, 4.57 mmol) were added in that order into a stirred and cooled (-78 °C) solution of **54.2** (450.1 mg, 2.28 mmol) in dry THF (20 mL) (Ar atmosphere). Stirring was continued for 10 min, the cold bath removed, and stirring was continued for an additional 20 min. The mixture was partitioned between water and EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.6 x 27 cm), using first hexane and then EtOAc-hexane mixtures up to 20% EtOAc, gave **54.3** (638.2 mg, 91%). **The compound must be used within ca 2 h, or stored at -78 °C**: FTIR ($CHCl_3$, cast) 2951, 2893, 2824, 2662, 1511, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.33 (td, J = 6.5, 0.6 Hz, 2 H), 3.48 (apparent t, J = 6.5 Hz, 2 H), 3.48 (s, 3 H), 3.77-4.20 (br s, 1 H), 5.08 (s, 2 H), 6.60 (apparent d, J = 8.9 Hz, 2 H), 6.93 (apparent d, J = 9.0 Hz, 2 H) (strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.2 (t), 46.9 (t), 55.9 (q), 95.6 (t), 114.5 (d), 118.1 (d), 141.9 (s), 150.2 (s); exact mass m/z calcd for $C_{10}H_{14}INO_2$ 307.00693, found 307.00756.

2,2,2-Trifluoro-*N*-(2-iodoethyl)-*N*-[4-(methoxymethoxy)phenyl]acetamide (54.4).

54.3 **54.4**

$(CF_3CO)_2O$ (0.52 mL, 3.7 mmol) was added into a stirred and cooled (0 °C) solution of fresh **54.3** (379.8 mg, 1.237 mmol) and *i*-Pr_2NEt (0.86 mL, 4.9 mmol) in CH_2Cl_2 (20 mL). Stirring at 0 °C was continued for 2 h, and the mixture was then partitioned between water and CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.6 x 24 cm), using first hexane and then 20% EtOAc-hexane, gave **54.4** (450.4 mg, 90%) as an oil: FTIR ($CHCl_3$, cast) 2960, 2829, 1702, 1587, 1510, 1443, 1151 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.21 (t, J = 7.8 Hz, 2 H), 3.48 (s, 3 H), 4.06 (t, J = 7.5 Hz, 2 H), 5.19 (s, 2 H), 7.06 (apparent dt, J = 8.9, 3.2 Hz, 2 H), 7.18 (apparent d, J = 8.6 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -1.9 (t), 53.5 (t), 56.2 (q), 94.4 (s), 116.2 (s split into q, J_{CF} = 286.8 Hz), 116.9 (d), 129.5 (d), 131.6 (s), 156.9 (s split into q, J_{CF} = 35.8 Hz), 157.8 (s); exact mass m/z calcd for $C_{12}H_{13}F_3INO_3$ 403.98923, found 402.98829.

2,2,2-Trifluoro-*N*-(4-hydroxyphenyl)-*N*-(2-iodoethyl)acetamide (54.5).

54.4 **54.5**

Me_3SiBr (0.17 mL, 1.3 mmol) was injected at a fast dropwise rate into a stirred solution of **54.4** (450.4 mg, 1.118 mmol) in dry CH_2Cl_2 (12 mL). Stirring was continued for 2.5 h, and another portion of Me_3SiBr (0.17 mL, 1.3 mmol) was injected. Stirring was

continued for 6 h and the mixture was quenched with water (10 mL). The aqueous layer was extracted twice with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 24 cm), using 20-30% EtOAc-hexane, gave **54.5** (320.8 mg, 80%): FTIR ($CHCl_3$, cast) 3391, 3031, 1674, 1611, 1597, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.23 (t, J = 7.8 Hz, 2 H), 4.08 (t, J = 7.5 Hz, 2 H), 5.23 (s, 2 H), 6.89 (apparent dt, J = 8.9, 3.4 Hz, 2 H), 7.16 (apparent d, J = 8.6 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ -2.1 (t), 53.3 (t), 116.2 (s split into q, J_{CF} = 286.8), 116.3 (d), 129.7 (d), 130.3 (s), 156.7 (s), 157.3 (s split into q, J_{CF} = 36.0 Hz); exact mass m/z calcd for $C_{10}H_9F_3INO_2$ 358.96301, found 358.96207.

2-[[4-(Methoxymethoxy)phenyl]amino]ethyl 4-Methylbenzenesulfonate (55.5) (Tentative structure).

54.2 **55.5**

TsCl (255.8 mg, 1.34 mmol) was added in one portion into a stirred solution of *i*-Pr_2NEt (0.23 mL, 1.3 mmol) and **54.2** (52.9 mg, 0.268 mmol) in THF (10 mL). Stirring was continued for 1 h and the reaction was quenched with water (5 mL). The mixture was partitioned between water and EtOAc, and the aqueous layer extracted with EtOAc. The combined organic extracts were washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.2 x 22 cm), using 50% EtOAc-hexane, gave **55.5** (98.2 mg, 100%): FTIR ($CHCl_3$, cast) 3536, 2927, 1599, 1507, 1344 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ

1.98 (br s, 1 H), 2.42 (s, 3 H), 3.44 (s, 3 H), 3.66 (br s, 4 H), 5.17 (s, 2 H), 6.97 (s, 4 H), 7.28 (d, J = 8.3 Hz, 2 H), 7.53 (apparent d, J = 8.3 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6 (q), 53.8 (q), 56.2 (t), 60.5 (t), 94.5 (t), 116.8 (d), 127.8 (d), 129.6 (d), 130.2 (d), 133.1 (s), 135.4 (s), 143.7 (s), 157.1 (s); exact mass m/z calcd for $C_{17}H_{21}NO_5S$ 351.11404, found 351.11396.

2-[(4-Hydroxyphenyl)amino]ethyl 4-Methylbenzenesulfonate (55.4) (Tentative structure).

55.5 **55.4**

Me_3SiBr (0.05 mL, 0.3 mmol) was injected at a fast dropwise rate into a stirred and cooled (0 °C) solution of **55.5** (98.2 mg, 0.280 mmol) in dry CH_2Cl_2 (5 mL). Stirring was continued for 7 h, and the mixture was quenched with water (10 mL). The aqueous layer was extracted twice with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 27 cm), using 50% EtOAc-hexane, gave **55.4** (54.1 mg, 63%): ^1H NMR ($CDCl_3$, 300 MHz) d 1.77-1.90 (br s, 1 H), 2.42 (s, 3 H), 3.66 (s, 4 H), 6.14 (br s, 1 H), 6.71 (apparent d, J = 8.9 Hz, 2 H), 6.89 (apparent d, J = 8.9 Hz, 2 H; strictly an AA'BB' system), 7.25-7.29 (m, 2 H), 7.52 (dm, J = 8.3 Hz, 2 H).

2-[(4-Oxocyclohexa-2,5-dienylidene)amino]ethyl 4-Methylbenzenesulfonate (57.2) (Tentative structure).

55.4 **57.2**

$PhI(OAc)_2$ (44.9 mg, 0.0806 mmol) was tipped into a stirred solution of freshly prepared **55.4** (16.5 mg, 0.0537 mmol) in dry MeOH (5 mL) (Ar atmosphere). Stirring was continued arbitrarily for 21 h, and the mixture was concentrated, and partitioned between EtOAc and water. The organic extract was washed with saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.2 x 22 cm), using 30% EtOAc-hexane, gave **57.2** (10.6 mg, 65%): ^1H NMR ($CDCl_3$, 500 MHz) δ 2.45 (s, 3 H), 3.73 (t, J = 6.1 Hz, 2 H), 4.17 (t, J = 6.2 Hz, 2 H), 6.19 (apparent d, J = 10.0 Hz, 2 H), 6.49 (apparent d, J = 10.1 Hz, 2 H; strictly an AA'BB' system), 7.32 (d, J = 8.4 Hz, 2 H), 7.69 (d, J = 8.3 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.0 (q), 47.7 (t), 65.2 (t), 127.5 (d), 129.6 (d), 129.8 (d), 135.9 (s), 143.3 (d), 144.4 (s), 185.2 (s).

***N*-(2-Iodoethyl-*N*-[4-(methoxymethoxy)phenyl]-4-methylbenzenesulfonamide (58.2).**

54.3 **58.2**

TsCl (321 mg, 1.68 mmol) was added in one portion into a stirred solution of *i*-Pr_2NEt (0.29 mL, 1.7 mmol) and **54.3** (258.4 mg, 0.8417 mmol) in THF (10 mL). Stirring was continued for 22 h and the reaction was quenched with water (5 mL). The mixture was

partitioned between water and EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 27 cm), using 20% EtOAc-hexane, gave **58.2** (286.7 mg, 74%): FTIR ($CHCl_3$, cast) 2956, 1598, 1505, 1442, 1348 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.43 (s, 3 H), 3.16 (apparent dd, J = 8.5, 6.8 Hz, 1 H), 3.48 (s, 3 H), 3.54 (apparent dd, J = 7.3, 6.5 Hz, 1 H), 3.79 (apparent dd, J = 7.3, 6.6 Hz, 1 H), 3.81 (apparent dd, J = 8.7, 7.6 Hz, 1 H), 5.16 (s, 2 H), 6.96 (s, 4 H), 7.27 (apparent dd, J = 7.9, 0.6 Hz, 2 H), 7.51 (apparent dd, J = 8.3, 4.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.53 (t), 21.6 (q), 41.2 (t), 52.7 (t), 53.7 (t), 56.2 (q), 94.4 (t), 116.7 (d), 127.67 (d), 127.71 (d), 129.50 (d), 129.52 (d), 130.3 (d), 132.2 (s), 132.5 (s), 135.31 (s), 135.34 (s), 143.7 (d), 157.09 (s), 157.11 (s); exact mass m/z calcd for $C_{17}H_{20}INO_4S$ 461.01578, found 461.01616.

***N*-(4-Hydroxyphenyl)-*N*-(2-iodoethyl-4-methylbenzenesulfonamide (58.3).**

58.2 **58.3**

Me_3SiBr (0.02 mL, 0.01 mmol) was injected at a fast dropwise rate into a stirred solution of **58.2** (20.5 mg, 0.0495 mmol) in dry CH_2Cl_2 (5 mL), and stirring was continued for 23 h. The mixture was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.3 x 27 cm), using 20% EtOAc-hexane and then 30% EtOAc-hexane, gave **58.3** (15.7 mg, 86%): FTIR ($CHCl_3$, cast) 3377, 1509, 1332, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.43 (s, 3 H), 3.17 (apparent dd, J = 8.0, 2.6 Hz, 1.6 H), 3.55 (t, J = 7.3 Hz, 0.4 H), 3.79 (t, J = 7.2 Hz, 0.4 H),

3.81 (apparent dd, J = 8.6, 7.5 Hz, 1.6 H), 4.97 (br s, 1 H), 6.75 (apparent dd, J = 8.8, 2.2 Hz, 2 H), 6.92 (apparent dd, J = 8.8, 2.2 Hz, 2 H; strictly an AA'BB' system), 7.26 (br d, J = 8.3 Hz, 2 H), 7.48-7.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (data for major isomer) δ 1.5 (t), 21.6 (q), 53.6 (t), 116.1 (d), 127.7 (d), 129.5 (d), 130.5 (d), 131.0 (s), 135.2 (s), 143.8 (s), 155.8 (s); exact mass m/z calcd for $C_{15}H_{16}INO_3S$ 416.98956, found 416.98964.

2,2,2-Trifluoro-*N*-(2-iodoethyl)-*N*-(1-methoxy-4-oxocyclohexa-2,5-dienyl)-acetamide (59.2).

54.5 **59.2**

(a) Use of $PhI(OAc)_2$

$PhI(OAc)_2$ (350.5 mg, 1.088 mmol) was tipped into a stirred solution of **54.5** (260.5 mg, 0.7230 mmol) in dry MeOH (15 mL). Stirring was continued for 50 h, and the solvents were then evaporated (water pump vacuum). The residue was partitioned between $CHCl_3$ and water, and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 23 cm), using first hexane and then EtOAc-hexane mixtures up to 30% EtOAc-hexane, gave **59.2** (219.7 mg, 78%): FTIR ($CHCl_3$, cast) 1703, 1673, 1223, 1199 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.30 (s, 3 H), 3.32-3.33 (br s, 1 H), 3.34 (s, 1 H), 3.96 (t, J = 8.0 Hz, 2 H), 6.43 (apparent AB q, J = 10.3 Hz, $\Delta\nu_{AB}$ = 24.2 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 1.2 (t), 45.9 (br t), 51.3 (q), 84.0 (q), 115.6 (s split into q, J_{CF} = 288.4 Hz), 132.5 (d), 141.9 (d), 184.1 (s); exact mass m/z calcd for $C_{11}H_{11}F_3INO_3$ 388.97357, found 388.97363.

(b) Use of $PhI(OCOCF_3)_2$

In another experiment, $PhI(OCOCF_3)_2$ (93.1 mg, 0.216 mmol) was tipped into a stirred solution of **54.5** (51.8 mg, 0.144 mmol) in dry MeOH (8 mL). Stirring was continued for 30 min, and the solvents were evaporated (water pump). The residue was partitioned between EtOAc and water, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 26 cm), using first hexane and then 20% EtOAc-hexane, gave **59.2** (29.8 mg, 53%) (the ^1H NMR spectrum on the crude material showed only grease as the impurity). A test showed that the compound is not fully extracted into EtOAc and may be partially lost during chromatography.

7a-Methoxy-1-trifluoroacetyl-1,2,3,3a,4,7a-hexahydroindol-5-one (59.3).

59.2 **59.3**

A solution of Bu_3SnH (0.19 mL, 0.73 mmol) and AIBN (10 mg, 0.06 mmol) in PhMe (5 mL) was added over 4 h by syringe pump into a stirred and heated (85 °C) solution of **59.2** (219.7 mg, 0.5648 mmol) in PhMe (15 mL). Heating at 85 °C was continued for 8 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.3 x 27 cm), using EtOAc-hexane mixtures from 0-50% EtOAc, gave **59.3**, which was slightly contaminated with tin species. The material was rechromatographed over silica gel (2.4 x 30 cm), using 20-40% EtOAc-hexane, to give **59.3** (80.2 mg, 54%; 64% after correction for recovered **59.2**) as an oil: FTIR ($CHCl_3$, cast) 2916, 2848, 1699, 1427, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.73 (ddt, J = 12.7, 7.9,

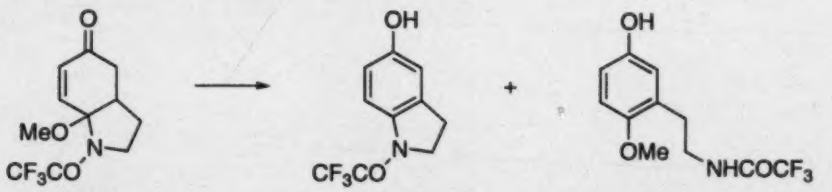
4.7 Hz, 1 H), 2.31-2.42 (m, 2 H), 2.59 (dd, J = 16.7, 5.6 Hz, 1 H), 2.86 (sextet, J = 4.6 Hz, 1 H), 3.39 (s, 3 H), 3.84 (apparent sextet, J = 4.0 Hz, 1 H), 3.92-3.99 (m, 1 H), 6.06 (d, J = 10.5 Hz, 1 H), 7.46 (d, J = 10.5, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.0 (t), 38.5 (t), 42.5 (d), 45.8 (m d), 51.6 (q), 93.4 (s), 115.9 (s split into q, J_{CF} = 288.8 Hz), 129.4 (d), 141.8 (d), 156.5 (s split into q, J_{CF} = 36.8 Hz), 196.5 (s); exact mass m/z calcd for $C_{11}H_{12}F_3NO_3$ 263.07693, found 263.07668.

1-(Trifluoroacetyl)-2,3-dihydro-1*H*-indol-5-ol (59.4).

59.3 **59.4**

TsOH.H_2O (20.3 mg) was added into a stirred mixture of **59.3** (*ca* 15 mg) and 4Å molecular sieves (*ca* 100 mg) in CH_2Cl_2 (5 mL), and stirring was continued for 2.5 h. The mixture was filtered and partitioned between water and $CHCl_3$. The combined organic extracts were dried and evaporated. The ^{1}H NMR spectrum showed that **59.4** was pure.

1-(Trifluoroacetyl)-2,3-dihydro-1*H*-indol-5-ol (59.4) and 2,2,2-Trifluoro-*N*-[2-(5-hydroxy-2-methoxyphenyl)ethyl]acetamide (59.5).



59.3 **59.4** **59.5**

TsOH.H_2O (12 mg) was added into a stirred solution of **59.3** (56.4 mg, 0.214 mmol) in CH_2Cl_2 (10 mL), and stirring was continued for 20 h. The mixture was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$, and the aqueous phase was extracted twice with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.6 x 25 cm), using hexane and then 30% EtOAc-hexane, gave **59.4** (30.5 mg, 62%) as an oil (sparingly soluble in $CHCl_3$) and **59.5** (3.5 mg, 6%). Compound **59.4** had: FTIR ($CHCl_3$, cast) 3347, 1667, 1616, 1605, 1493, 1462 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 3.17 (t, J = 8.1 Hz, 2 H), 4.24 (t, J = 8.6 Hz, 2 H), 6.63 (apparent dd, J = 8.8, 2.5 Hz, 1 H), 6.71-6.73 (m, 1 H), 7.92 (d, J = 8.8 Hz, 1 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 29.4 (t), 49.4 (t), 112.9 (d), 114.7 (d), 117.8 (s split into q, J_{CF} = 286.0 Hz), 119.6 (d), 135.2 (s), 135.5 (s), 154.5 (s split into q, J_{CF} = 37.1 Hz), 157.2 (s); exact mass m/z calcd for $C_{10}H_8F_3NO_2$ 231.05072, found 231.05061. Compound **59.5** had: FTIR ($CHCl_3$, cast) 3016, 2979, 2916, 2848, 2351, 1683, 1610, 1600, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.24 (t, J = 8.3 Hz, 2 H), 3.81, (s, 3 H), 4.28 (td, J = 8.5, 0.9 Hz, 2 H), 6.79 (dd, J = 8.8, 2.7 Hz, 1 H), 6.81-6.83 (m, 1 H), 8.13 (d, J = 8.8 Hz, 1 H); exact mass m/z calcd for $C_{11}H_{10}F_3NO_2$ 245.06636, found 245.06649. A ^{13}C NMR spectrum was not measured.

2-[(4-Hydroxyphenyl)amino]ethanol (60.2).[59]

60.1 **60.2**

An oven-dried round-bottomed flask containing a magnetic stirring bar was capped by a septum and allowed to cool under an Ar stream. The septum was removed

momentarily, and phenol **60.1** (510 mg, 2.32 mmol) was added. Ethanolamine (2.8 mL, 4.6 mmol) was injected, and oven-dried K_2CO_3 (640 mg, 4.6 mmol), followed by CuI (88 mg, 0.46 mmol) and L-proline (107 mg, 0.93 mmol) were tipped in, again by momentarily removing the septum. Dry DMSO (2 mL) was injected and the mixture was lowered into an oil bath preset at 60 °C and the mixture was stirred for 30 h (Ar atmosphere). The resulting brownish orange mixture was cooled to room temperature and poured into a conical flask. Water (*ca* 30 mL) was added and the mixture was carefully acidified to pH 7 with 10% hydrochloric acid (pH paper), and then carefully saturated with solid NaCl. After the vigorous reaction had subsided, the mixture was extracted with EtOAc (4 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 21 cm), using EtOAc, gave **60.2** (267 mg, 75%). Compound **60.1** (19.5 mg, 3.8%) was also recovered.

In a second experiment, an oven-dried round-bottomed flask containing a magnetic stirring bar was capped by a septum and allowed to cool under an Ar stream. The septum was removed momentarily, and phenol **60.1** (682 mg, 3.10 mmol) was tipped in. Ethanolamine (0.93 mL, 15.5 mmol) and dry DMSO (2 mL) were injected. Oven-dried K_2CO_3 (856 mg, 6.2 mmol), CuI (118 mg, 0.62 mmol) and L-proline (143 mg, 1.2 mmol) were tipped in, again by momentarily removing the septum. The mixture was lowered into an oil bath preset at 55 °C and the mixture was stirred for 3 h (Ar atmosphere). The mixture was cooled to room temperature and poured into a conical flask. Water (*ca* 30 mL) was added and the mixture was carefully acidified to pH 7 with 10% hydrochloric acid (pH paper), and then carefully saturated with solid NaCl. After the vigorous reaction had subsided, the mixture was extracted with EtOAc (4 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 18 cm), using EtOAc, gave **60.2** (386 mg, 81%).

Allyl (2-Hydroxyethyl)(4-hydroxyphenyl)carbamate (62.2).

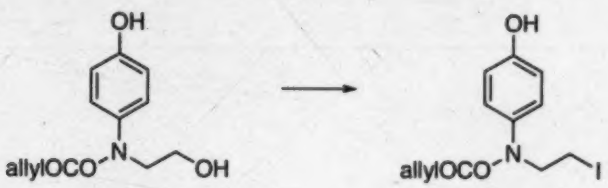
60.2 **62.2**

AllylOCOCl (0.13 mL, *ca* 1.2 mmol, 0.6 equiv) was injected at a fast dropwise rate into a stirred and cooled (-40 °C) solution of **60.2** (310.3 mg, 2.028 mmol) in dry MeCN (20 mL) (Ar atmosphere). Stirring was continued for 4 min, and the cooling bath was removed. After an additional 5 min, dry *i*-Pr_2NEt (0.21 mL, *ca* 1.2 mmol, 0.6 equiv) was injected rapidly and stirring was continued for 2 min. The mixture was recooled to -40 °C and a second portion of allylOCOCl (0.13 mL, *ca* 1.2 mmol, 0.6 equiv) was injected. Stirring was continued for 5 min, and the cold bath was removed. Stirring was continued for 7 min, and water (10 mL) was added. The mixture was concentrated under water pump vacuum (rotary evaporator) to remove most of the organic solvent, and the residue was partitioned between $CHCl_3$ and brine. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.4 x 27 cm), using EtOAc-hexane mixtures from 20% to 100% EtOAc, gave **62.2** (299.0 mg, 62%) as an oil: FTIR (CH_2Cl_2, cast) 3338, 2945, 1774, 1515, 1451, 1409 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.75-3.81 (m, 4 H), 4.58 (br s, 2 H), 5.12 (br s, 2 H), 5.83 (br s, 2 H), 6.73 (br s, 2 H), 6.82 (br s, 2 H), 7.04 (apparent d, J = 8.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 116.1 (br t), 128.6 (s), 132.4 (s), 133.9 (d), 155.2 (d); exact mass m/z calcd for $C_{12}H_{15}NO_4$ 237.10011, found 237.09218.

The following simpler procedure was used in a subsequent experiment: AllylOCOCl (0.18 mL, *ca* 1.7 mmol, 1.1 equiv) was injected at a fast dropwise rate into a stirred solution of **60.2** (236.5 mg, 1.546 mmol) in dry MeCN (10 mL) (Ar atmosphere). The mixture became highly colored and a precipitate formed. Stirring was continued for 1 h

and water (10 mL) was added. The mixture was partitioned between $CHCl_3$ and brine, and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 25 cm), using EtOAc-hexane mixtures from 20% to 100% EtOAc, gave **62.2** (203.8 mg, 56%) as an oil.

Allyl (2-Iodoethyl)(4-hydroxyphenyl)carbamate (62.3).



62.2 **62.3**

Imidazole (324 mg, 4.76 mmol), Ph_3P (887 mg, 3.39 mmol), and then I_2 (328 mg, 3.26 mmol) were added in that order into a stirred solution of **62.2** (297.3 mg, 1.254 mmol) in dry THF (20 mL) (Ar atmosphere). Stirring was continued for 22 min, and the mixture was partitioned between $CHCl_3$ and a 1:1:1:4 mixture of brine, saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$ and water. The aqueous layer was extracted twice with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.6 x 26 cm), using first hexane and then 1:3-EtOAc-hexane, gave **62.3** (380.0 mg, 87%): FTIR ($CHCl_3$, cast) 3337, 1674, 1646, 1515, 1448, 1408 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.20 (t, J = 7.6 Hz, 2 H), 3.97 (t, J = 7.5 Hz, 2 H), 4.57 (br s, 1 H), 4.69 (br s, 1 H), 5.12 (br s, 1 H), 5.24-5.44 (br m, 1 H), 5.76-6.02 (br m, 1 H), 6.24 (br s, 0.5 H), 6.63-6.88 (br m, 2.5 H), 7.03 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 1.1 (t), 52.8 (t), 115.6-116.6 (m of d), 130.0 (m of d), 132.2 (d), 132.5 (m of s); exact mass m/z calcd for $C_{12}H_{14}INO_3$ 347.00183, found 347.00282.

Allyl (2-Iodoethyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamate (63.2).

62.3 **63.2**

$PhI(OAc)_2$ (404.7 mg, 1.257 mmol) was tipped into a stirred solution of **62.3** (358.2 mg, 1.047 mmol) in dry MeOH (20 mL) (Ar atmosphere). Stirring was continued for 54 min, and the reaction was quenched with a 1:1 solution of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted three times with $CHCl_3$, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.4 x 27 cm), using first 20% EtOAc-hexane and then 30% EtOAc-hexane, gave **63.2** (368.3 mg, 93%): FTIR ($CHCl_3$, cast) 2939, 1756, 1710, 1673, 1633, 1396 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.23 (s, 3 H), 3.26-3.29 (m, 2 H), 3.82-3.86 (m, 2 H), 4.54 (dt, *J* = 5.7, 1.4 Hz, 2 H), 5.23 (do, *J* = 10.4, 1.5 Hz, 1 H), 5.27 (do, *J* = 17.2, 1.5 Hz, 1 H), 5.85 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1 H), 6.34 (apparent d, *J* = 10.2 Hz, 2 H), 6.59 (apparent d, *J* = 10.2 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.2 (t), 45.9 (t), 51.2 (q), 66.5 (t), 82.8 (s), 118.4 (s), 130.4 (d), 131.8 (d), 144.3 (d), 153.6 (s), 184.8 (s); exact mass *m/z* calcd for $C_{13}H_{16}INO_4$ 377.01243, found 377.01206.

Allyl 7a-Methoxy-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylate (63.3).

63.2 **63.3**

A solution of Bu_3SnH (0.27 mL, 1.0 mmol) and AIBN (*ca* 10 mg, 0.06 mmol) in PhMe (5 mL) was added over 3 h by syringe pump into a stirred and heated (90 °C) solution of **63.2** (329.2 mg, 0.8732 mmol) in PhMe (15 mL). Heating at 90 °C was continued for 12 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.6 x 28 cm), using EtOAc-hexane mixtures from 20% to 50% EtOAc, gave **63.3** (150.4 mg, 69%) as an oil: FTIR (CH_2Cl_2, cast) 2953, 2899, 1705, 1647, 1452, 1389 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.56-1.62 (m, 1 H), 2.24-2.42 (br m, 2 H), 2.46-2.58 (br m, 1 H), 2.81 (br s, 0.75 H), 2.88 (br s, 0.25 H), 3.29 (br s, 0.75 H), 3.34 (s, 2.25 H), 3.61 (td, J = 9.1, 3.1 Hz, 1 H), 3.74 (apparent dd, J = 18.5, 8.6 Hz, 1 H), 4.52-4.71 (m, 2 H), 5.22 (d, J = 10.3 Hz, 1 H), 5.31 (apparent d, J = 17.2 Hz, 1 H), 5.93 (ddt, J = 17.1, 10.5, 5.6 Hz, 1 H), 6.00 (d, J = 10.4, 1 H), 7.16 (br d, J = 6.7 Hz, 0.25 H), 7.45 (d, J = 10.2 Hz, 0.75 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.2 (t), 39.3 (t), 43.8 (d), 46.2 (t), 50.9 (q), 66.0 (t), 90.7 (s), 117.8 (t), 128.2 (d), 132.5 (d), 144.2 (d), 154.4 (s), 197.7 (s); exact mass *m/z* calcd for $C_{13}H_{17}NO_4$ 251.11575, found 251.11518.

Allyl 5-Hydroxy-2,3-dihydroindole-1-carboxylate (63.4).

63.3 **63.4**

$TsOH.H_2O$ (5.3 mg) was added into a stirred mixture of **63.3** (45.4 mg, 0.181 mmol) and 4Å molecular sieves (*ca* 100 mg) in dry CH_2Cl_2 (10 mL). The initially light yellow solution immediately became colorless, and stirring was continued overnight. The mixture was filtered through Celite and evaporated. Flash chromatography of the residue over silica gel (1.2 x 23 cm), using 30% EtOAc-hexane, gave **63.4** (38.0 mg, 96%) as an oil:

FTIR ($CHCl_3$, cast) 3360, 2950, 1670, 1604, 1497, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.06 (t, J = 7.5 Hz, 2 H), 4.03 (t, J = 8.5 Hz, 2 H), 4.70 (br s, 1.3 H), 4.78 (br s, 0.7 H), 5.23-5.41 (br m, 2 H), 5.70 (br s, 1 H), 5.99 (br s, 1 H), 6.66 (d, J = 8.4 Hz, 1 H), 6.70-6.71 (m, 1 H), 7.34 (br s, 0.4 H), 7.67-7.73 (br m, 0.6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.6 (m t), 47.5 (m t), 65.8 (m t), 112.2 (m d), 113.8 (d), 117.6 (m s), 132.7 (m d), 135.9 (m t); exact mass m/z calcd for $C_{12}H_{12}NO_3$ 219.08954, found 219.08958.

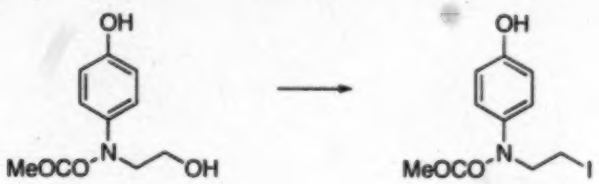
Methyl (2-hydroxyethyl)(4-hydroxyphenyl)carbamate (64.2).

60.2 **64.2**

MeOCOCl (0.06 mL, *ca* 0.9 mmol, 0.6 equiv.) was injected at a fast dropwise rate into a stirred and cooled (-30 °C) solution of **60.2** (214.1 mg, 1.399 mmol) in MeCN (10 mL) (Ar atmosphere). Stirring was continued for 25 min, producing an orange precipitate. Dry *i*-Pr_2NEt (0.15 mL, *ca* 0.85, 0.6 equiv.) was injected rapidly and the cold bath removed. Stirring was continued for 20 min, and the mixture was recooled to -30 °C and a second portion of MeOCOCl (0.06 mL, *ca* 0.9 mmol, 0.6 equiv.) was injected. Stirring was continued for 1 h 20 min, as the bath slowly reached room temperature. Brine (*ca* 20 mL) was added and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was kept under oil pump vacuum for 3 h, and flash chromatography over silica gel (2.4 x 23 cm), using EtOAc, gave **64.2** (206.1 mg, 70%): FTIR (microscope) 3333, 2957, 1678, 1597, 1516, 1461, 1393 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 3.56-3.74 (br s, 3 H), 3.61 (t, J = 5.9 Hz, 2 H), 3.68 (t, J = 6.3 Hz, 2 H), 6.76 (d, J = 8.6 Hz, 2 H), 7.05 (apparent br d, J = 5.9 Hz, 2 H); ^{13}C NMR

(CD_3OD, 100 MHz) δ 53.3 (q), 53.8 (t), 60.1 (t), 116.6 (d), 129.9 (d), 134.7 (s), 157.6 (s), 158.7 (s); exact mass *m/z* calcd for $C_{10}H_{13}NO_4$ 211.08446, found 211.08404.

Methyl (4-hydroxyphenyl)(2-iodoethyl)carbamate (64.3).



64.2 **64.3**

Imidazole (470 mg, 7.0 mmol), Ph_3P (1.28 g, 3.90 mmol), and I_2 (1.19 g, 4.71 mmol) were added in that order into a stirred solution of **64.2** (397.7 mg, 1.885 mmol) in dry THF (14 mL) (Ar atmosphere). Stirring was continued for 1 h 40 min, and the mixture was partitioned between $CHCl_3$ and a 1:1:1 mixture of brine, saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted twice with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.4 x 28 cm), using first hexane, then 20% EtOAc-hexane, and finally 50% EtOAc-hexane, gave **64.3** (515.2 mg, 85%): FTIR ($CHCl_3$, cast) 3305, 2953, 1675, 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.16-3.23 (br m, 2 H), 3.62-3.86 (apparent br d, 3 H), 3.92-3.98 (br m, 2 H), 6.62 (br m, 2 H), 7.02 (apparent br d, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 1.0 (t), 52.8 (t), 53.3 (q), 116.0 (m d), 121.4 (d), 128.6 (br d), 132.8 (s), 155.4 (br s); exact mass *m/z* calcd for $C_{10}H_{12}INO_3$ 320.98621, found 320.98637.

Methyl (2-Iodoethyl)(1-methoxy-4-oxocyclohexa-2,5-dienyl)carbamate (64.4).

64.3 **64.4**

$PhI(OAc)_2$ (556 mg, 1.73 mmol) was tipped into a stirred solution of freshly prepared **64.3** (462.3 mg, 1.440 mmol) in dry MeOH (20 mL) (Ar atmosphere). Stirring was continued for 30 min, and the reaction was quenched with a 1:1 solution of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted three times with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.4 x 22 cm), using first hexane, then 25% EtOAc-hexane and finally 50% EtOAc-hexane, gave **64.4** (469.2 mg, 93%): FTIR ($CHCl_3$, cast) 2952, 1712, 1672, 1633, 1455, 1383 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.28 (s, 3 H), 3.28-3.32 (m, 2 H), 3.71 (s, 3 H), 3.83-3.87 (m, 2 H), 6.40 (apparent d, J = 10.2 Hz, 2 H), 6.63 (apparent d, J = 10.2 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 3.3 (t), 45.9 (t), 51.3 (q), 52.9 (q), 82.8 (s), 130.4 (d), 144.4 (d), 154.5 (s), 184.9 (s); exact mass m/z calcd for $C_{11}H_{14}INO_4$ 350.99677, found 350.99633.

Methyl 7a-Methoxy-5-oxo-2,3,3a,4,5,7a-hexahydroindole-1-carboxylate (64.5).

64.4 **64.5**

A solution of Bu_3SnH (0.21 mL, 0.79 mmol) and AIBN (19.8 mg, 0.121 mmol) in

PhMe (5 mL) was added over 3 h by syringe pump into a stirred and heated (90 °C) solution of **64.4** (232.2 mg, 0.6615 mmol) in PhMe (15 mL) (Ar atmosphere). Heating at 90 °C was continued for 1.5 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.4 x 30 cm), using EtOAc-hexane mixtures from 30% to 50% EtOAc, gave **64.5** (115.2 mg, 77%) as an oil: FTIR ($CHCl_3$, cast) 2955, 1703, 1445, 1367 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.58 (ddd, *J* = 12.1, 8.4, 4.3 Hz, 1 H), 2.16-2.42 (br m, 2 H), 2.46-2.58 (br m, 1 H), 2.77-2.92 (br m, 1 H), 3.26-3.36 (br s, 3 H), 3.55-3.62 (br m, 1 H), 3.65-3.78 (br m, 1 H), 3.71 (br s, 3 H), 5.99 (d, *J* = 10.3 Hz, 1 H), 7.08-7.16 (br s, 0.3 H), 7.46 (d, *J* = 9.9 Hz, 0.7 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1 (t), 39.3 (t), 43.8 (d), 46.2 (t), 50.3 (br q), 52.6 (q), 128.2 (m d), 144.1 (d), 155.2 (s), 197.6 (m s); exact mass *m/z* calcd for $C_{11}H_{15}NO_4$ 225.10011, found 225.09948.

Methyl 5-Hydroxy-2,3-dihydroindole-1-carboxylate (64.6).

64.5 **64.6**

$TsOH.H_2O$ (4.2 mg) was added into a stirred mixture of **64.5** (33.5 mg, 0.149 mmol) and 4Å molecular sieves (*ca* 20 mg) in CH_2Cl_2 (10 mL), and stirring was continued for 4.5 h. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1.2 x 22 cm), using 50% EtOAc-CH_2Cl_2, gave **64.6** (24.0 mg, 83%) as an oil: FTIR (microscope) 3275, 2961, 1708, 1671, 1600, 1484 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 3.02 (t, *J* = 8.6 Hz, 2 H), 3.74-3.86 (br s, 3 H), 3.93 (t, *J* = 8.4 Hz, 2 H), 6.56 (dd, *J* = 8.6, 2.4 Hz, 1 H), 6.63 (apparent t, *J* = 1.3 Hz, 1 H), 7.18-7.32 (br s, 0.3 H), 7.48-7.60 (br s, 0.7 H); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ 28.2 (br t), 47.5 (br t), 52.2 (q), 112.9 (d),

114.0 (d), 115.7 (br d), 154.0 (s); exact mass *m/z* calcd for $C_{10}H_{11}NO_3$ 193.07390, found 193.07356.

2-Hydroxy-*N*-(4-hydroxyphenyl)propionamide (65.2).

60.1 **65.2**

(*S*)-(-)-Lactamide (566 mg, 6.35 mmol) and Cs_2CO_3 (1.38 g, 4.23 mmol) were tipped into an oven-dried round-bottomed flask containing **60.1** (465.8 mg, 2.117 mmol) (Ar atmosphere). DMF (3 mL), CuI (80.4 mg, 0.423 mmol) and *N,N'*-dimethylethylene-diamine (0.09 ml, 0.8 mmol) were added in that order. The mixture was lowered into an oil bath (65 °C) and stirred for 2 h. The mixture was cooled to room temperature and filtered through a pad of silica gel (2 x 3 cm), using 20% MeOH-EtOAc (100 mL) as a rinse. The filtrate was evaporated and the residue was kept under oil pump vacuum for 1.5 h. Flash chromatography of the residue over silica gel (2.6 x 28 cm), using EtOAc, gave **65.2** (308.8 mg, 80%): FTIR (microscope) 3324, 1650, 1605, 1538, 1516, 1445 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.41 (d, *J* = 6.8 Hz, 3 H), 4.22 (q, *J* = 6.8 Hz, 1 H), 4.76-4.97 (br s, 1 H), 6.74 (apparent d, *J* = 8.8 Hz, 2 H), 7.34 (apparent d, *J* = 8.8 Hz, 2 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 21.2 (q), 69.4 (d), 116.3 (d), 123.7 (d), 130.8 (s), 155.7 (s), 175.8 (s); exact mass *m/z* calcd for $C_9H_{11}NO_3$ 181.07390, found 181.07383.

2-Iodo-*N*-(4-hydroxyphenyl)propionamide (65.3).

65.2 **65.3**

Imidazole (178.7 mg, 2.628 mmol), Ph_3P (715.2 mg, 2.739 mmol), and I_2 (513.6 mg, 2.022 mmol) were added in that order into a stirred solution of **65.2** (183.0 mg, 1.011 mmol) in dry CH_2Cl_2 (10 mL) (Ar atmosphere). Stirring at room temperature was continued for 4.5 h, and the mixture was then refluxed for 24 h. The mixture was cooled to room temperature and partitioned between $CHCl_3$ and a 1:1:1 mixture of brine, saturated aqueous $Na_2S_2O_3$ and water. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.6 x 28 cm), using first 25% EtOAc-hexane and then 50% EtOAc-hexane, gave **65.3** (210.5 mg, 71%): FTIR (microscope) 3301, 3070, 1650, 1608, 1547, 1512 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 1.92 (d, J = 6.9 Hz, 3 H), 4.71 (q, J = 6.8 Hz, 1 H), 4.85 (br s, 1 H), 6.74 (apparent dt, J = 8.9, 2.0 Hz, 2 H), 7.32 (apparent dt, J = 8.9, 2 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3 (d), 24.1 (q), 116.3 (d), 123.1 (d), 131.3 (s), 155.6 (s), 171.9 (s); exact mass m/z calcd for $C_9H_{10}INO_2$ 290.97562, found 290.97566.

***N*-(1-Methoxy-4-oxocyclohexa-2,5-dienyl)acetamide (56.4).**

56.3 **56.4**

PhIO (208.5 mg, 0.948 mmol) was tipped into a stirred solution of **56.3** (119.3 mg, 0.7901 mmol) in dry MeOH (5 mL). After 2.5 h, $TsOH.H_2O$ (1.1 mg) was added and stirring was continued for 15 min. The solvent was gently concentrated to *ca* 2.5 mL (water pump vacuum). Flash chromatography of the residue over silica gel (1.8 x 23 cm), using first 1% MeOH-EtOAc and then increasing amounts of MeOH up to 5% MeOH-EtOAc, gave **56.4** (132.2 mg, 92%).

2-Iodo-*N*-(1-methoxy-4-oxocyclohexa-2,5-dienyl)propionamide (66.3).

65.3 **66.3**

PhIO (101.9 mg, 0.4632 mmol) was tipped into a stirred solution of **65.3** (109.9 mg, 0.3776 mmol) in dry MeOH (8 mL). After 45 min, $TsOH.H_2O$ (0.6 mg) was added and stirring was continued for 10 min. The solvent was gently concentrated to *ca* 1 mL (water pump vacuum). Flash chromatography of the residue over silica gel (1.6 x 21 cm), using EtOAc-hexane-MeOH mixtures from 10:90:1 to 50:50:1 EtOAc-hexane-MeOH, gave **66.3** (91.8 mg, 75%). This material, which was stable as a solid and in MeOH solutions, contained *ca* 10% of a minor isomer. The major isomer had: FTIR (microscope) 3296, 3045, 2935, 1673, 1637, 1536 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 1.81 (d, J = 6.9 Hz, 3 H), 3.28 (s, 3 H), 4.56 (q, J = 6.9 Hz, 1 H), 4.80 (s, 1 H), 6.28-6.33 (m, 2 H), 6.98-7.01 (m, 2 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 16.9 (d), 23.7 (q), 51.3 (q), 80.5 (s), 130.86 (d), 130.89 (d), 145.8 (d), 146.1 (d), 186.7 (s); exact mass m/z calcd for $C_{10}H_{12}INO_3$ 320.98621, found 321.98627.

Formation of 2-iodo-*N*-(4-hydroxyphenyl)propionamide by attempted radical cyclization of 66.3.

66.3 **65.2**

A solution of Bu_3SnH (0.09 mL, 0.35 mmol) and AIBN (*ca* 10 mg, 0.06 mmol) in MeOH (4 mL) was added over 2 h by syringe pump into a stirred and refluxing solution of **66.3** (86.2 mg, 0.268 mmol) and $TsOH.H_2O$ (3.2 mg) in MeOH (6 mL). Heating was continued for 1.5 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.4 x 27 cm), using 50% EtOAc-hexane, gave crude **65.2** (40.9 mg) as a solid. Recrystalization from $CHCl_3$ gave pure **65.2** (23.1 mg) as a white solid.

[1-[(4-Methoxymethoxy)phenyl)]piperidin-2-yl]methanol (68.2).

54.1 **68.2**

2-Piperidinemethanol (1.37 g, 11.9 mmol) was added into an oven-dried round-bottomed flask containing **54.1** (1.5723 g, 5.955 mmol) (Ar atmosphere). Oven-dried K_2CO_3 (1.64 g, 11.9 mmol), CuI (226 mg, 1.19 mmol) and L-proline (274 mg, 2.38 mmol) were tipped in. Dry DMSO (5 mL) was injected and the flask was lowered into an oil bath

preset at 80 °C and the mixture was stirred for 26 h, cooled to room temperature and partitioned between water and $CHCl_3$. The aqueous layer was extracted twice with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was dried under oil pump vacuum. Flash chromatography of the residue over silica gel (2.8 x 26 cm), using first hexane and then 30% EtOAc-hexane, gave **68.2** (421.2 mg, 28%): FTIR ($CHCl_3$, cast) 3350, 2934, 1722, 1509, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50-1.82 (m, 6 H), 1.98 (br s, 1 H), 3.06 (t, J = 5.2 Hz, 2 H), 3.41 (quintet, J = 5.0 Hz, 1 H), 3.47 (s, 3 H), 3.51 (dd, J = 10.9, 5.5 Hz, 1 H), 3.59 (dd, J = 10.9, 5.5 Hz 1 H), 6.99 (apparent AB q, J = 9.2 Hz, $\Delta\nu_{AB}$ = 22.3 Hz, 4 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (t), 25.0 (t), 26.4 (t), 49.9 (t), 55.8 (q), 59.3 (t), 61.4 (d), 94.9 (t), 117.1 (d), 121.5 (d), 146.2 (s), 152.1 (s); exact mass m/z calcd for $C_{14}H_{21}NO_3$ 251.15215, found 251.15225.

2-Iodomethyl-1-[(4-methoxymethoxy)phenyl]piperidine (68.3).

68.2 **68.3**

Imidazole (60.3 mg, 0.887 mmol), Ph_3P (267.2 mg, 1.019 mmol), and I_2 (225.2 mg, 0.8868 mmol) were added in that order into a stirred solution of **68.2** (110.3 mg, 0.4394 mmol) in dry THF (10 mL) (Ar atmosphere). Stirring was continued for 45 min, and the reaction was quenched with water (5 mL). Saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ were added and the mixture was partitioned between water and $CHCl_3$. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 25 cm), using first hexane and then 10% EtOAc-hexane,

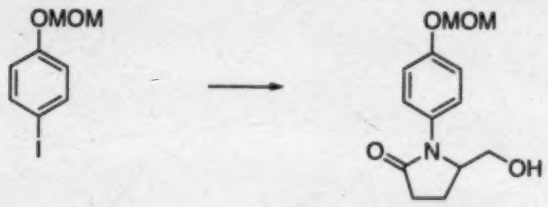
gave **68.3**, which was contaminated with Ph_3PO and was therefore used directly in the next step.

4-[(2-Iodomethyl)piperidin-1-yl]phenol (68.4).

68.3 **68.4**

Me_3SiBr (0.17 mL, 1.3 mmol) was injected at a fast dropwise rate into a stirred solution of the above crude **68.3** in dry CH_2Cl_2 (10 mL). Stirring was continued for 13 h and a second portion of Me_3SiBr (0.080 mL, 1.3 mmol) was added. After 15 min the mixture was quenched with water (10 mL) and, after an additional 45 min, the mixture was neutralized with $NaHCO_3$, and brine (20 mL) was added. The aqueous layer was extracted three times with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 26 cm), using EtOAc-hexane mixtures from 100% hexane to 30% EtOAc-hexane, gave **68.4** (57.5 mg, 41% over two steps): FTIR ($CHCl_3$, cast) 3291, 2926, 2853, 1509, 1445, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) d 1.54-1.80 (br m, 4 H), 1.87-2.04 (br m, 2 H), 2.94-3.06 (br s, 2 H), 3.11-3.23 (m, 1 H), 3.35-3.63 (m, 2 H), 5.16 (br s, 1 H), 6.78 (br d, J = 7.1 Hz, 2 H), 6.94 (apparent br d, J = 6.3 Hz, 2 H); exact mass m/z calcd for $C_{12}H_{17}INO$ (M + H) 318.03494, found 318.03555. The 13C NMR spectrum was unsatisfactory as the signals were very broad.

5-Hydroxymethyl-1-[4-(methoxymethoxy)phenyl]pyrrolidin-2-one (69.3).



54.1 **69.3**

DMF (3 mL) was injected into an oven-dried round-bottomed flask containing **54.1** (606.1 mg, 2.296 mmol) and amide **69.2** (0.80 g, 6.9 mmol) (Ar atmosphere). Cs_2CO_3 (1.496 g, 4.592 mmol) and CuI (87.2 mg, 0.459 mmol) were tipped in, and *N,N'* dimethylethylenediamine (0.10 ml, 0.92 mmol) was injected. The mixture was lowered into an oil bath (80 °C) and stirred for 30 h. The mixture was cooled to room temperature and filtered through a pad of silica gel (2 x 3 cm), using 20% MeOH-EtOAc (100 mL) as a rinse. The filtrate was evaporated and the residue was kept overnight under oil pump vacuum. Flash chromatography of the residue over silica gel (2.6 x 28 cm), using MeOH-EtOAc mixtures from 0% to 10% MeOH, gave **69.3** (411.1 mg, 71%): FTIR (CH_2Cl_2, cast) 3391, 2950, 1668, 1607, 1511, 1409 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.04-2.12 (m, 1 H), 2.15-2.25 (m, 1 H), 2.38-2.46 (m, 1 H), 2.60 (ddd, J = 17.1, 10.1, 7.6 Hz, 1 H), 3.08 (br s, 1 H), 3.43 (s, 3 H), 3.44-3.56 (m, 2 H), 5.11 (AB q, J = 6.9 Hz, $\Delta\nu_{AB}$ = 4.4 Hz, 2 H), 7.00 (apparent dt, J = 9.0, 2.2 Hz, 2 H), 7.21 (apparent dt, J = 9.0, 2.2 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0 (t), 31.3 (t), 55.9 (q), 61.8 (d), 62.0 (t), 94.5 (t), 116.8 (d), 126.2 (d), 131.2 (s), 155.5 (s), 175.5 (s); exact mass m/z calcd for $C_{13}H_{17}NO_4$ 251.11575, found 251.11562.

5-Iodomethyl-1-[4-(methoxymethoxy)phenyl]pyrrolidin-2-one (69.4).

69.3 **69.4**

Imidazole (104.8 mg, 1.542 mmol), Ph_3P (262.6 mg, 1.002 mmol), and I_2 (254.5 mg, 1.002 mmol) were added in that order into a stirred solution of **69.3** (193.5 mg, 0.7710 mmol) in dry THF (10 mL) (Ar atmosphere). Stirring was continued for 1.5 h, and the reaction was quenched with water (5 mL). Saturated aqueous $Na_2S_2O_3$ was added and the mixture was partitioned between brine and $CHCl_3$. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.6 x 28 cm), using first 50% EtOAc-hexane and then EtOAc, gave **69.4** (267.2 mg, 96%): FTIR ($CHCl_3$, cast) 2953, 1694, 1510, 1392, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.92-2.00 (m, 1 H), 2.35-2.43 (m, 1 H), 2.50-2.56 (m, 1 H), 2.73 (tt, J = 10.6, 6.7 Hz, 1 H), 3.16 (dd, J = 10.5, 6.5 Hz, 1 H), 3.31 (dd, J = 10.5, 2.5 Hz, 1 H), 3.47 (s, 3 H), 4.12 (tt, J = 4.7, 4.1 Hz, 1 H), 5.16 (AB q, J = 6.9 Hz, $\Delta\nu_{AB}$ = 4.4 Hz, 2 H), 7.07 (apparent dt, J = 9.0, 2.3 Hz, 2 H), 2.26 (apparent dt, J = 9.0, 2.0 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.2 (t), 24.6 (t), 30.5 (t), 55.9 (q), 59.5 (d), 90.4 (t), 116.9 (d), 126.4 (d), 130.3 (s), 155.7 (s), 174.1 (s); exact mass m/z calcd for $C_{13}H_{16}INO_3$ 361.01749, found 361.01839.

1-(4-Hydoxyphenyl)-5-(iodomethyl)pyrrolidin-2-one (69.5).

69.4 **69.5**

Me_3SiBr (0.22 mL, 1.7 mmol) was injected at a fast dropwise rate into a stirred solution of **69.4** (264.1 mg, 0.7316 mmol) in dry CH_2Cl_2 (10 mL). Stirring was continued for 30 min, and the mixture was quenched with water (10 mL). The aqueous layer was extracted three times with EtOAc, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 26 cm), using EtOAc and then 5% MeOH-EtOAc, gave **69.5** (170.1 mg, 73%): FTIR (microscope) 3057, 2981, 2815, 1639, 1595, 1509 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.69-1.77 (m, 1 H), 2.21-2.29 (m, 1 H), 2.33-2.39 (m, 1 H), 2.48 (quintet, J = 1.8 Hz, 1 H), 2.48-2.55 (m, 1 H), 3.20 (dd, J = 10.6, 5.6 Hz, 1 H), 3.30 (s, 1 H), 3.35 (dd, J = 10.6, 2.3 Hz, 1 H), 4.11-4.16 (m, 1 H), 6.77 (apparent d, J = 8.9 Hz, 2 H), 7.16 (apparent d, J = 8.9 Hz, 2 H; strictly an AA'BB' system), 9.42 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9 (t), 23.7 (t), 30.0 (t), 58.1 (d), 115.2 (d), 126.2 (d), 127.9 (s), 155.3 (s), 172.9 (s); exact mass m/z calcd for $C_{11}H_{12}INO_2$ 316.99127, found 316.99091.

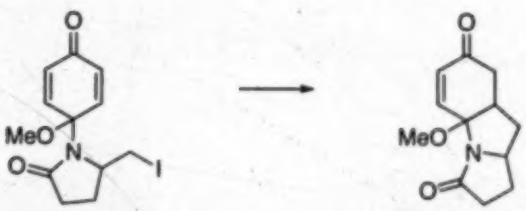
5-Iodomethyl-1-(1-methoxy-4-oxocyclohexa-2,5-dienyl)pyrrolidin-2-one (69.6).

69.5 **69.6**

$PhI(OAc)_2$ (112.5 mg, 0.3494 mmol) was tipped into a stirred solution of **69.5** (97.0 mg, 0.2795 mmol) in dry MeOH (10 mL). Stirring was continued for 30 min, and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.8 x 26 cm), using first 50% EtOAc-hexane and then EtOAc, gave **69.6** (86.4 mg, 89%): FTIR ($CHCl_3$, cast) 2939, 1697, 1672, 1634, 1456, 1386 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.00

(apparent dt, J = 9.5, 1.7 Hz, 1 H), 2.18-2.28 (m, 2 H), 2.57-2.67 (m, 1 H), 3.22 (2 overlapping s, 3 H), 3.37 (dd, J = 10.0, 7.7 Hz, 1 H), 3.49 (dd, J = 10.0, 2.4 Hz, 1 H), 4.17 (tm, J = 8.5 Hz, 1 H), 6.39 (apparent dt, J = 10.3, 1.0 Hz, 2 H), 6.58 (dm, J = 9.2 Hz, 1 H), 6.76 (dm, J = 10.3 Hz, 1 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.3 (t), 25.2 (t), 30.3 (t), 50.9 (q), 57.3 (d), 82.1 (s), 131.1 (d), 131.4 (d), 143.1 (d), 143.8 (d), 173.9 (s), 184.6 (s); exact mass m/z calcd for $C_{12}H_{14}INO_3$ 347.00183, found 347.00228.

3b-Methoxy-1,2,7,7a,8,8a-hexahydro-3b*H*-3a-azacyclopenta[*a*]indene-3,6-dione (69.7).



69.6 **69.7**

A solution of Bu_3SnH (0.08 mL, 0.28 mmol) and AIBN (10 mg, 0.06 mmol) in PhMe (5 mL) was added over 4 h by syringe pump into a stirred and heated (85 °C) solution of **69.6** (80.8 mg, 0.233 mmol) in PhMe (15 mL). Heating at 85 °C was continued for 8 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.6 x 30 cm) using EtOAc, gave **69.7** (42.9 mg, 83%) as an oil: FTIR (CH_2Cl_2, cast) 2938, 1694, 1457, 1390, 1346, 1326 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (dt, J = 9.3, 11.9 Hz, 1 H), 1.64-1.73 (m, 1 H), 2.23 (quintet, J = 6.3 Hz, 1 H), 2.26-2.32 (m, 1 H), 2.41 (dd, J = 12.7, 4.1, 1 H), 2.43-2.49 (m, 1 H), 2.68-2.76 (m, 1 H), 2.75 (dd, J = 16.7, 6.5 Hz, 1 H), 2.98-2.34 (m, 1 H), 3.49 (s, 3 H), 4.20 (tt, J = 9.4, 6.0 Hz, 1 H), 6.05 (apparent dt, J = 10.5, 0.8 Hz, 1 H), 7.66 (dm, J = 10.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.9 (t), 35.9 (t), 36.9 (t), 38.7 (t), 46.4 (d), 52.0 (q), 61.4 (d), 87.6 (s),

128.6 (d), 140.8 (d), 174.5 (s), 196.9 (s); exact mass *m/z* calcd for $C_{12}H_{15}NO_3$ 221.10519, found 221.10554.

6-Hydroxy-1,2,8,8a-tetrahydro-3a-azacyclopenta[*a*]inden-3-one (69.8).

69.7 **69.8**

TsOH.H_2O (4.3 mg) was added into a stirred mixture of **69.7** (29.3 mg, 0.132 mmol) and 4Å molecular sieves (*ca* 20 mg) in CH_2Cl_2 (10 mL), and stirring was continued for 40 min. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1.2 x 29 cm), using EtOAc, gave **69.8** (20.5 mg, 82%) as an a white solid: FTIR (microscope) 3203, 2975, 1651, 1610, 1500, 1453 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 1.94-2.02 (m, 1 H), 2.44 (quintet of m, *J* = 7.3 Hz, 1 H), 2.50 (ddd, *J* = 16.6, 8.6, 0.7 Hz, 1 H), 2.79-2.90 (m, 2 H), 3.10 (dd, *J* = 15.7, 8.2 Hz, 1 H), 3.30 (quintet, *J* = 1.6 Hz, 2 H), 4.64 (tdd, *J* = 9.8, 8.3, 6.2 Hz, 2 H), 6.60 (dd, *J* = 8.4, 2.5 Hz, 1 H), 6.67-6.69 (m, 1 H), 7.29 (d, *J* = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.8 (t), 36.7 (t), 37.2 (t), 65.4 (d), 113.8 (d), 114.5 (d), 116.2 (d), 132.6 (s), 138.0 (s), 156.1 (s); exact mass *m/z* calcd for $C_{11}H_{11}NO_2$ 189.07898, found 189.07917.

2-[4-(Methoxymethoxy)phenylamino]butan-1-ol (70.2).

54.1 **70.2**

2-Amino-1-butanol (1.62 mL, 17.2 mmol) was injected into an oven-dried round-bottomed flask containing **54.1** (1.1348 g, 4.298 mmol) (Ar atmosphere). Oven-dried K_2CO_3 (1.186 g, 8.596 mmol), CuI (163 mg, 0.860 mmol) and L-proline (198 mg, 1.72 mmol) were tipped in. Dry DMSO (4 mL) was injected and the flask was lowered into an oil bath preset at 80 °C and the mixture was stirred for 14 h. The mixture was cooled to room temperature and partitioned between water and $CHCl_3$. The aqueous layer was extracted twice with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.6 x 29 cm), using EtOAc-hexane mixtures from 0% to 50% EtOAc, gave **70.2** (755.5 mg, 78%): FTIR ($CHCl_3$, cast) 3385, 2960, 1511, 1463, 1227, 1196 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, J = 7.5 Hz, 3 H), 1.55 (quintet, J = 7.4 Hz, 2 H), 2.25-3.10 (br s, 2 H), 3.31 (dt, J = 10.6, 4.4 Hz, 1 H), 3.47 (s, 3 H), 3.48 (dd, J = 5.0, 6.1 Hz, 1 H), 3.73 (dd, J = 10.9, 4.1 Hz, 1 H), 5.07 (s, 2 H), 6.61 (apparent d, J = 8.9, 2 H), 6.90 (apparent d, J = 8.7 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.5 (q), 24.9 (t), 55.8 (d), 57.7 (q), 64.0 (t), 95.5 (t), 115.1 (d), 118.0 (d), 143.1 (s), 149.8 (s); exact mass m/z calcd for $C_{12}H_{19}NO_3$ 225.13649, found 225.13653.

2,2,2-Trifluoro-*N*-(1-iodomethylpropyl)-*N*-[(4-methoxymethoxy)phenyl-acetamide (71.2).

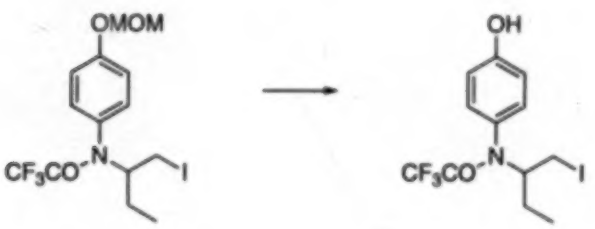
70.2 **71.2**

Imidazole (405 mg, 5.95 mmol), Ph_3P (1.62 g, 6.18 mmol), and I_2 (1.16 g, 4.58 mmol) were added in that order into a stirred and cooled (-78 °C) solution of **70.2** (515.1 mg, 2.289 mmol) in dry THF (20 mL) (Ar atmosphere). Stirring was continued for 3 min, the cold bath was removed, and stirring was continued for 12 min. The mixture was partitioned between water and EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated. This material was used directly in the next step.

$(CF_3CO)_2O$ (0.96 mL, 6.8 mmol) was added into a stirred and cooled (-50 °C, acetone-dry ice) solution of the above crude mixture and *i*-Pr_2NEt (1.59 mL, 9.16 mmol) in CH_2Cl_2 (30 mL). Stirring was continued for 7 h, during which time the mixture slowly reached room temperature (after *ca* 2 h). The mixture was partitioned between water and $CHCl_3$ and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.4 x 28 cm), using first hexane and then EtOAc-hexane mixtures up to 30% EtOAc-hexane, gave **71.2**. Flash chromatography of this material over silica gel (2.4 x 28 cm), using first hexane and then EtOAc-hexane mixtures up to 30% EtOAc-hexane, gave **71.2** (923.2 mg, 94%) as an oil, which appeared to be a 1:1 mixture of rotamers: FTIR ($CHCl_3$, cast) 2924, 2850, 1699, 1510, 1192, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, J = 7.3 Hz, 1.5 H), 1.04 (t, J = 7.3 Hz, 1.5 H), 1.51-1.60 (m, 0.5 H), 1.61-1.69 (m, 0.5 H), 1.75 (quintet, J = 7.2 Hz, 1 H), 2.99 (dd, J = 10.6, 10.1 Hz, 0.5 H), 3.27 (dd, J = 10.8, 4.7 Hz, 0.5 H), 3.49 (s, 3 H), 3.96-4.03 (m, 1 H), 4.21-4.28 (m, 0.5 H), 4.80 (septet, J = 4.4 Hz, 0.5 H),

5.19 (s, 2 H), 7.03-7.08 (m, 2 H), 7.11-7.15 (m, 0.5 H), 7.17-7.26 (br s, 1 H), 7.47 (br d, J = 8.4 Hz, 0.5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 5.0 (t), 11.3 (q), 14.0 (q), 25.6 (t), 30.0 (t), 32.7 (d), 56.2 (q), 58.5 (t), 61.4 (d), 94.41 (t), 116.33 (d), 116.33 (s split into q, J_{CF} = 287.9 Hz), 116.38 (d), 116.38 (s split into q, J_{CF} = 288.4 Hz), 116.8 (d), 127.6 (s), 129.6 (d), 131.1 (d), 131.3 (d), 131.7 (s), 157.5 (s split into q, J_{CF} = 35.8 Hz), 157.9 (s), 158.0 (s); exact mass *m/z* calcd for $C_{14}H_{17}F_3INO_3$ 431.02054, found 431.01996.

2,2,2-Trifluoro-*N*-(4-hydroxyphenyl)-*N*-(1-iodomethylpropyl)acetamide (71.3).

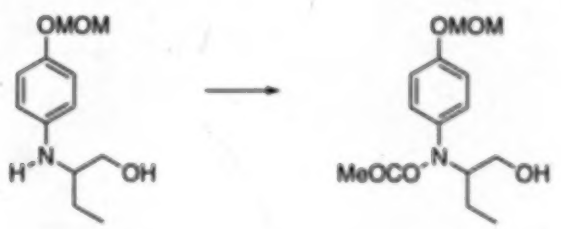


71.2 **71.3**

Me_3SiBr (0.62 mL, 4.7 mmol) was injected at a fast dropwise rate into a stirred and cooled (-78 °C) solution of **71.2** (890.1 mg, 2.065 mmol) in dry CH_2Cl_2 (25 mL). After 2 min the cooling bath was removed and stirring was continued for 6 h. Another portion of Me_3SiBr (0.10 mL, 0.7 mmol) was injected, stirring was continued for an additional 18 h and the mixture was quenched with water (2 mL), and partitioned between water and $CHCl_3$. The aqueous layer was extracted twice with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.4 x 28 cm), using first hexane and then 10-20% EtOAc-hexane, gave **71.3** (794.6 mg, 99%) as a 1:1 mixture of rotamers: FTIR ($CHCl_3$, cast) 3391, 2970, 1674, 1596, 1514, 1443 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (two superimposed t, J = 7.0 and 7.2 Hz, 3 H), 1.50-1.69 (m, 1 H), 1.76 (apparent quintet, J = 7.0 Hz, 1 H), 2.96 (t, J = 10.7 Hz, 0.5 H), 3.28 (dd, J = 10.8, 4.3 Hz, 0.5 H), 3.89-4.02 (m, 1 H), 4.33 (dd, J = 13.4,

8.0 Hz, 0.5 H), 4.85 (tt, J = 9.9, 5.5 Hz, 0.5 H), 6.77 (br s, 1 H), 6.90-6.95 (m, 2 H), 7.06-7.10 (br m, 0.5 H), 7.17 (br s, 1 H), 7.42-7.46 (br m, 0.5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.8 (t), 11.3 (q), 13.9 (q), 25.7 (t), 30.1 (t), 32.5 (d), 58.5 (t), 61.5 (d), 115.9 (d), 116.3 (d), 116.4 (two s, each split into q, J_{CF} = 287.2 Hz), 125.7 (s), 129.6 (d), 129.9 (s), 131.1 (d), 131.3 (d), 156.9 (s), 157.2 (s), 158.1 (s split into q, J_{CF} = 32.7 Hz); exact mass m/z calcd for $C_{12}H_{13}F_3INO_2$ 386.99432, found 386.99424.

Methyl [(1-Hydroxymethyl)propyl][4-(methoxymethoxy)phenyl]-carbamate (72.2).

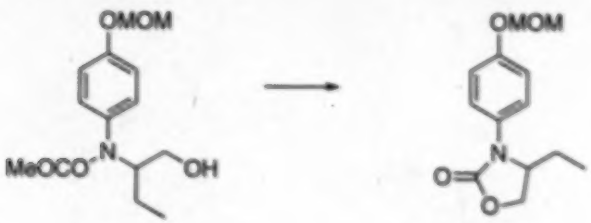


70.2 **72.2**

Saturated aqueous $NaHCO_3$ (5 mL) and MeOCOCl (0.19 mL, 2.5 mmol) were added into a stirred and cooled (0 °C) solution of **70.2** (*ca* 100 mg, 0.5 mmol) in $CHCl_3$. Additional portions of MeOCOCl (0.19 mL) were added after 4 h and 6 h. Stirring was continued for 13 h after the last addition, and the mixture was diluted with water and extracted twice with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was kept under oil pump vacuum for 3 h, and flash chromatography over silica gel (1.8 x 24 cm), using 50% EtOAc-hexane, gave **72.2** (81.0 mg, *ca* 60%): FTIR ($CHCl_3$, cast) 3451, 2961, 1701, 1685, 1510, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (t, J = 7.3 Hz, 3 H), 1.38-1.47 (m, 2 H), 2.45-2.62 (br s, 1 H), 3.48 (s, 3 H), 3.46-3.53 (m, 1 H), 3.63 (br s, 3 H), 3.70 (dd, J = 11.5, 3.5 Hz, 1 H), 4.16-4.24 (m, 1 H), 5.18 (s, 2 H), 7.01 (apparent dt, J = 9.0, 3.2 Hz, 2 H), 7.13 (apparent dt, J = 9.0, 3.2 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.2 (q), 22.2

(t), 52.9 (t), 56.1 (t), 62.5 (d), 63.5 (t), 94.5 (t), 116.4 (d), 130.3 (d), 132.6 (s), 156.4 (s), 157.9; exact mass *m/z* calcd for $C_{14}H_{21}NO_5$ 283.14197, found 283.14228.

4-Ethyl-3 [4-(Methoxymethoxy)phenyl]oxazolidin-2-one (72.3)



72.2 **72.3**

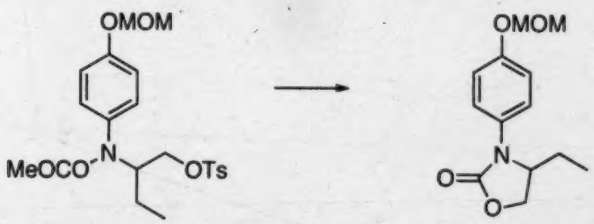
Imidazole (48.1 mg, 0.707 mmol), Ph_3P (192.5 mg, 0.7347 mmol), and I_2 (138.2 mg, 0.5442 mmol) were added in that order into a stirred and cooled (-78 °C) solution of **72.2** (77.0 mg, 0.2721 mmol) in dry THF (10 mL) (Ar atmosphere). The cold bath was removed after 1 min and stirring was continued for 50 min. The mixture was partitioned between $CHCl_3$ and a 1:1:1 mixture of brine, saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted twice with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 26 cm), using first 30% EtOAc-hexane and then 50% EtOAc-hexane, gave **72.3** (56.4 mg, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.5 Hz, 3 H), 1.54-1.63 (m, 1 H), 1.66-1.74 (m, 1 H), 3.47 (s, 3 H), 4.11 (dd, J = 18.5, 5.8 Hz, 1 H), 4.26-4.34 (m, 1 H), 4.53 (t, J = 8.5 Hz, 1 H), 5.16 (apparent s, 2 H), 7.05 (apparent d, J = 8.9 Hz, 2 H), 7.30 (apparent d, J = 8.9 Hz, 2 H; strictly an AA'BB' system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.8 (q), 24.7 (t), 55.9 (q), 57.7 (d), 66.4 (t), 94.6 (t), 116.9 (d), 124.3 (d), 130.6 (s), 155.0 (s), 156.3 (s).

2-[Methoxycarbonyl[[4-(methoxymethoxymethyl)phenyl]amino]]butyl 4-Methylbenzenesulfonate (73.2).

70.2 **73.2**

Dry *i*-Pr_2NEt (0.078 mL, 0.45 mmol) and then MeOCOCl (0.035 mL, 0.45 mmol) were injected into a stirred and cooled (0 °C) solution of **70.2** (92.1 mg, 0.409 mmol) in CH_2Cl_2 (10 mL) (Ar atmosphere). The cold bath was left in place but not recharged, and stirring was continued overnight. Dry Et_3N (0.3 mL, 0.13 mmol) and TsCl (233.9 mg, 1.228 mmol) were added and stirring was continued for 12 h. The mixture was quenched with MeOH (0.5 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.4 x 26 cm), using first 30% EtOAc-hexane and then 50% EtOAc-hexane, gave **73.2** (91.5 mg, 51%): ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (t, *J* = 7.3 Hz, 3 H), 1.37-1.45 (m, 1 H), 1.47-1.58 (m, 1 H), 2.46 (s, 3 H), 3.49 (s, 3 H), 3.58 (br s, 3 H), 4.00-4.03 (m, 1 H), 4.06 (br s, 1 H), 4.25 (tt, *J* = 7.7, 6.0 Hz, 1 H), 5.16 (s, 2 H), 6.94-7.02 (m, 4 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 7.79 (apparent d, *J* = 8.3 Hz, 2 H).

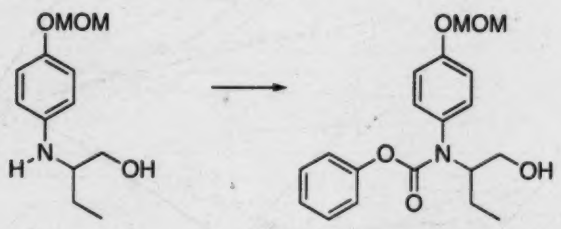
4-Ethyl-3 [4-(Methoxymethoxy)phenyl]oxazolidin-2-one (73.3).



73.2 **73.3**

A stirred solution of **73.2** (91.5 mg, 0.209 mmol) and NaI (471.1 mg, 3.141 mmol) in dry acetone (10 mL) was stirred at room temperature for 1 h, refluxed for 24 h, then stirred for an additional 18 h at room temperature. The mixture was partitioned between $CHCl_3$ and a 1:1 mixture of water and saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted twice with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. The ^1H NMR spectrum showed that the material was almost exclusively **73.3**.

Phenyl [(1-Hydroxymethyl)propyl][4-(methoxymethoxy)phenyl]-carbamate (76.2).

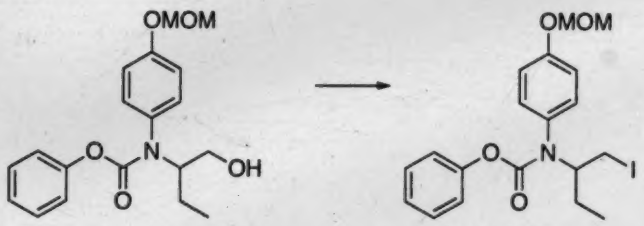


70.2 **76.2**

PhOCOCl (0.19 mL, *ca* 1.5 mmol) was injected at a fast dropwise rate into a stirred and cooled (-30 °C, acetone-dry ice) solution of **70.2** (301.7 mg, 1.341 mmol) and *i*-Pr_2NEt (0.27 mL, 1.5 mmol) in CH_2Cl_2. After 15 min the cold bath was removed and stirring was continued for an additional 85 min. Saturated aqueous $NaHCO_3$ (20 mL) was added and, after 30 min, the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.6 x 26 cm), using EtOAc-hexane mixtures from 20% to 50% EtOAc, gave **76.2** (377.2 mg, 81%) as an oil: FTIR ($CHCl_3$, cast) 3478, 2965, 1719, 1593, 1511, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (t, J = 7.1 Hz, 3 H), 1.41-1.56 (m, 2 H), 2.65 (br s, 1 H), 3.49 (s, 3 H), 3.50-3.56 (m, 1 H), 3.66-3.74 (m, 1 H), 4.28 (br s, 1 H), 5.18 (s, 2 H), 7.05 (apparent d, J = 8.9 Hz, 3 H), 7.15 (t, J = 7.2 Hz, 1 H), 7.26-7.33 (m, 4 H); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 11.1 (q), 22.4 (br t), 56.0 (q), 62.8 (d), 63.1 (t), 94.4 (t), 116.4 (d), 121.5 (d), 125.1 (d), 129.0 (d), 130.2 (d), 132.2 (s), 132.2 (s), 151.3 (s), 156.5 (s); exact mass *m/z* calcd for $C_{19}H_{23}NO_5$ 345.15762, found 345.15864.

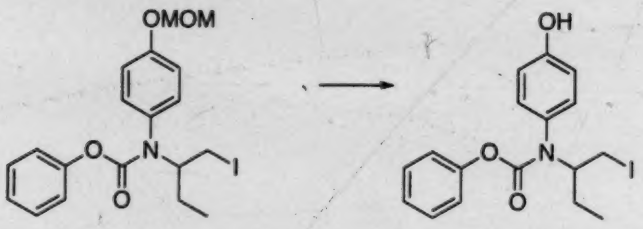
Phenyl [(1-Iodomethyl)propyl][4-(methoxymethoxy)phenyl]-carbamate (76.3).



76.2 **76.3**

Imidazole (255.0 mg, 3.750 mmol), Ph_3P (698.0 mg, 2.664 mmol), and I_2 (651.6 mg, 2.565 mmol) were added in that order into a stirred and cooled (0 °C) solution of **76.2** (340.4 mg, 0.9867 mmol) in dry THF (20 mL). The cold bath was removed after 1 h and stirring was continued for 40 min. The mixture was quenched with brine (10 mL) and saturated aqueous $Na_2S_2O_3$ (10 mL), and then partitioned between $CHCl_3$ and water. The aqueous layer was extracted twice with $CHCl_3$ and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.8 x 28 cm), using 20% EtOAc-hexane, gave **76.3** (401.1 mg, 89%): FTIR ($CHCl_3$, cast) 2964, 1720, 1592, 1510, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, *J* = 6.0 Hz, 3 H), 1.62-1.78 (m, 2 H), 3.15-3.25 (br m, 1 H), 3.36 (dd, *J* = 10.5, 4.9 Hz, 1 H), 3.50 (s, 3 H), 7.07 (apparent d, *J* = 9.0 Hz, 2 H), 7.09-7.10 (m, 2 H), 7.28-7.36 (m, 2 H), 7.36 (apparent d, *J* = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.4 (br t), 11.7 (q), 26.1 (br t), 56.2 (q), 62.4 (d), 94.5 (t), 116.6 (d), 121.7 (d), 125.3 (d), 129.2 (d), 130.4 (d), 131.6 (br s), 151.4 (s), 154.7 (s), 156.9 (s); exact mass *m/z* calcd for $C_{19}H_{22}INO_4$ 455.05936, found 455.05904.

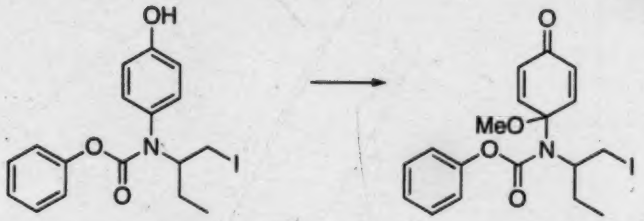
Phenyl (4-Hydroxyphenyl)[(1-iodomethyl)propyl]carbamate (76.4).



76.3 **76.4**

Me_3SiBr (0.05 mL, 0.4 mmol) was injected at a fast dropwise rate into a stirred solution of **76.3** (77.9 mg, 0.177 mmol) in dry CH_2Cl_2 (6 mL). After 1 h the reaction mixture was quenched with water (5 mL), and then partitioned between water and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.8 x 28 cm), using 20% EtOAc-hexane and then 50% EtOAc-hexane, gave **76.4** (57.1 mg, 81%): FTIR ($CHCl_3$, cast) 3359, 2959, 2921, 2851, 1716, 1689 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07-1.20 (br m, 3 H), 1.58-1.72 (m, 2 H), 3.02-3.18 (br m, 1 H), 3.30-3.36 (m, 1 H), 4.48 (br s, 0.7 H), 4.62 (br s, 0.3 H), 5.79 (br s, 0.6 H), 6.44 (br s, 0.4 H), 6.62 (br s, 0.6 H), 6.74-6.82 (br m, 1 H), 7.02-7.40 (br m, 7 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 7.3 (br t), 11.6 (br q), 26.1 (br t), 62.3 (br d), 115.9 (br d), 116.3 (br d), 121.6 (br t), 125.3 (br t), 119.3 (br t), 129.8 (br s), 130.3 (d), 151.3 (br s), 154.9 (br s), 155.6 (br s); exact mass *m/z* calcd for $C_{17}H_{18}INO_3$ 411.03314, found 411.03381.

Phenyl [1-(Iodomethyl)propyl](1-methoxy-4-oxocyclohexa-2,5-dienyl)-carbamate (76.5).



76.4 **76.5**

$PhI(OAc)_2$ (50.3 mg, 0.1562 mmol) was tipped into a stirred and cooled (0 °C) solution of **76.4** (50.0 mg, 0.125 mmol) in dry MeOH (10 mL). After 20 min, the cold bath was removed and stirring was continued for 1.5 h. The reaction was quenched with a 1:1 mixture (20 mL) of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The mixture was extracted three times with $CHCl_3$, and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 24 cm), using first 10% EtOAc-hexane and then 20% EtOAc-hexane, gave **76.5** (51.5 mg, 93%): FTIR ($CHCl_3$, cast) 2966, 2934, 1721, 1673, 1633, 1321 cm^{-1}; exact mass *m/z* calcd for $C_{18}H_{20}INNaO_4$ (M + Na) 464.03293, found 464.03312. Satisfactory ^1H and ^{13}C NMR spectra could not be obtained, as the compound decomposes on attempted concentration of its solutions.

Phenyl 2-Ethyl-7a-methoxy-5-oxo-2,3,3a,4,5,7a-hexahydro-indole-1-carboxylate (76.6).

76.5 **76.6**

A solution of Bu_3SnH (0.05 mL, 0.16 mmol) and AIBN (*ca* 10 mg, 0.06 mmol) in PhMe (5 mL) was added over 2 h by syringe pump into a stirred and heated (85 °C)

solution of **76.5** (56.9 mg, 0.129 mmol) in PhMe (10 mL). Heating at 85 °C was continued for 10 h after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.6 x 28 cm), using EtOAc-hexane mixtures from 20% to 50% EtOAc, gave **76.6** (31.8 mg, 78%): FTIR ($CHCl_3$, cast) 2958, 2923, 2851, 1717, 1699, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (the material is a mixture of diastereoisomers, each of which appears to be a mixture of rotamers) δ 0.86-1.02 (m, 3 H), 1.43-1.72 (m, 2 H), 1.82-1.90 (m, 0.2 H), 2.03-2.14 (m, 0.2 H), 2.15-2.27 (m, 0.5 H), 2.28-2.43 (m, 0.6 H), 2.59 (dd, *J* = 16.5, 6.3 Hz, 0.5 H), 2.69-2.77 (m, 0.2 H), 2.81-2.98 (br m, 0.6 H), 3.39 (s, 0.9 H), 3.45 (s, 0.9 H), 3.76 (s, 1.2 H), 3.96-4.20 (m, 1 H), 5.24-5.37 (br m, 0.3 H), 6.01 (d, *J* = 10.3 Hz, 0.4 H), 6.07 (d, *J* = 10.4 Hz, 0.4 H), 6.76 (dd, *J* = 16.1, 9.2 Hz, 2 H), 7.10-7.42 (m, 5 H); exact mass *m/z* calcd for $C_{18}H_{21}NNaO_4$ (M + Na) 338.13628, found 338.13514. The ^{13}C NMR spectrum was too complex to have diagnostic value.

Phenyl 2-Ethyl-5-hydroxy-2,3-dihydroindole-1-carboxylate (76.7).

76.6 **76.7**

$TsOH.H_2O$ (3.2 mg) was added into a stirred mixture of **76.6** (30.2 mg, 0.0959 mmol) and 4Å molecular sieves (*ca* 50 mg) in $CHCl_3$ (5 mL). Stirring was continued for 15 min, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1.8 x 26 cm), using first hexane, then 20% EtOAc-hexane, and finally 50% EtOAc-hexane, gave **76.7** (16.3 mg, 71%) as an oil: FTIR ($CHCl_3$, cast) 3380, 2966, 2876, 1716, 1689, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (br t, *J* = 5.5 Hz, 3 H), 1.58-1.78 (br m, 2 H), 1.85-1.95 (br s, 1 H), 2.72-2.82 (br d, 1 H), 3.35 (br dd, *J* = 15.5, 10.0 Hz,

1 H), 4.50-4.63 (apparent br s, 1 H), 4.97 (br s, 1 H), 6.61 (dd, J = 9.0, 2.5 Hz, 1 H), 6.68 (br s, 1 H), 7.17-7.25 (m, 3 H), 7.39 (t, J = 8.0 Hz, 2.3 H), 7.64-7.71 (br s, 0.55 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 9.1 (q), 27.8 (br t), 33.3 (t), 61.2 (br d), 112.2 (br d), 113.9 (d), 116.2 (br d), 121.8 (d), 125.5 (d), 129.4 (d), 135.5 (br s), 150.9 (br s), 152.0 (s); exact mass m/z calcd for $C_{17}H_{17}NO_3$ 283.12085, found 283.12038.

Methyl 5-Allyl-2,3-dihydroindole-1-carboxylate (77.3).

63.3 **77.3**

Allyl magnesium bromide (0.72 mL, 1 M in THF, 0.72 mmol) was added at a fast dropwise rate into a stirred and cooled (-78 °C) solution of **63.3** (70.6 mg, 0.289 mmol) in THF (10 mL) (Ar atmosphere). After 5 min, the cold bath was removed and stirring was continued for 15 min. The reaction was quenched with water (5 mL) and the mixture was partitioned between $CHCl_3$ and water. The aqueous phase was extracted twice with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in CH_2Cl_2 (10 mL) and 4Å molecular sieves (*ca* 70 mg) and $TsOH.H_2O$ (5.1 mg) were added with stirring. Stirring was continued overnight, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1.2 x 26 cm), using first hexane and then 20% EtOAc-hexane, gave **77.3** (50.1 mg, 71%) as an oil: FTIR ($CHCl_3$, cast) 3078, 2921, 1710, 1638, 1615, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.10 (t, J = 8.6 Hz, 2 H), 3.34 (d, J = 6.6 Hz, 2 H), 4.04 (t, J = 8.6 Hz, 2 H), 4.68-4.83 (br m, 2 H), 5.03-5.09 (m, 2 H), 5.24-5.41 (br m, 2 H), 5.95 (ddt, J = 17.0, 10.2, 6.6 Hz, 1 H), 5.95-6.07 (br s, 1 H), 6.98-7.03 (br s, 1 H), 7.00 (s, 1 H), 7.38-7.52 (br s, 0.35 H), 7.76-

7.83 (br s, 0.65 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.5 (br t), 39.7 (t), 47.5 (br t), 114.5 (br d), 115.5 (t), 117.6 (br s), 124.8 (br d), 127.6 (d), 132.7 (br d), 134.4 (t), 137.8 (d); exact mass *m/z* calcd for $C_{15}H_{17}NO_2$ 243.12593, found 243.12527.

Methyl 4-Allyl-2,3,3a,4,5,7a-hexahydro-7a-methoxy-5-oxo-indole-1-carboxylate (78.2).

64.4 **78.2**

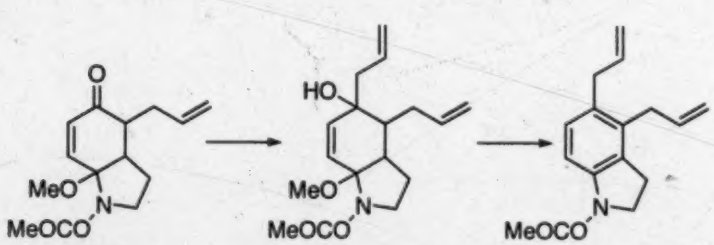
A stirred solution of allyltributyltin (0.42 mL, 1.3 mmol), AIBN (22.1 mg, 0.135 mmol) and **64.4** (237.0 mg, 0.6752 mmol) in PhMe (10 mL) was refluxed for 24 h (Ar atmosphere). The solution was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (3.6 x 30 cm), using EtOAc-hexane mixtures from 30% to 50% EtOAc, gave **78.2** (109.8 mg, 61%) as an oil: FTIR ($CHCl_3$, cast) 2954, 1708, 1639, 1445, 1367 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (the material is a mixture of diastereomers, each of which is a mixture of rotamers) δ 1.70-1.84 (br m, 1 H), 1.86-1.99 (m, 0.6 H), 2.06-2.44 (br m, 2.6 H), 2.57-2.70 (br m, 1.4 H), 2.77-2.96 (m, 1 H), 3.20-3.34 (m, 0.8 H), 3.69 (br s, 1 H), 3.52-3.57 (m, 0.8 H), 3.60-3.82 (br m, 4.8 H), 5.02-5.14 (m, 2 H), 5.66-5.83 (m, 1 H), 5.92-6.02 (m, 1 H), 6.90-7.20 (m, 0.4 H), 7.40-7.46 (m, 0.6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.5 (br t), 30.5 (t), 31.9 (br t), 44.7 (d), 45.8 (t), 46.1 (br t), 46.3 (br d), 46.7 (br d), 50.6 (q), 52.5 (br q), 52.8 (q), 117.2 (t), 117.6 (br t), 127.8 (m d), 130.3 (d), 135.0 (d), 135.4 (d), 143.1 (br d), 144.3 (d), 155.0 (s); exact mass *m/z* calcd for $C_{14}H_{19}NO_4$ 265.13141, found 265.13110.

Methyl 4-Allyl-5-hydroxy-2,3-dihydroindole-1-carboxylate (78.3).

78.2 **78.3**

$TsOH.H_2O$ (3.8 mg) was added into a stirred mixture of **78.2** (41.0 mg, 0.155 mmol) and 4Å molecular sieves (*ca* 20 mg) in CH_2Cl_2 (10 mL). Stirring was continued for 19 h, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1.2 x 27 cm), using hexane, then 20% EtOAc-hexane, and finally 35% EtOAc-hexane, gave **78.3** (28.9 mg, 80%) as an oil: FTIR (microscope) 3353, 3074, 2959, 2915, 1682, 1638, 1601, 1484 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 2.97 (t, J = 8.6 Hz, 2 H), 3.27-3.31 (m, 2 H), 3.72-3.84 (br s, 3 H), 3.92 (t, J = 8.1 Hz, 2 H), 4.91 (t, J = 1.3 Hz, 1 H), 4.94 (apparent dq, J = 7.4, 1.7 Hz, 1 H), 5.87 (dddd, J = 16.8, 10.7, 6.5, 6.1 Hz, 1 H), 6.58 (d, J = 8.5 Hz, 1 H), 7.04-7.20 (br s, 0.3 H), 7.38-7.46 (br s, 0.7 H); ^{13}C NMR (CD_3OD, 125 MHz) δ 27.2 (br t), 32.1 (t), 52.9 (br q), 113.9 (br d), 114.4 (d), 115.0 (t), 124.2 (s), 133.0 (br s), 136.0 (br s), 136.9 (d), 152.2 (s); exact mass m/z calcd for $C_{13}H_{15}NO_3$ 233.10519, found 233.10544.

Methyl 4,5-Diallyl-2,3-dihydroindole-1-carboxylate (78.5).



78.2 **78.4** **78.5**

Allylmagnesium bromide (0.20 mL, 1 M in THF, 0.20 mmol) was added at a fast

dropwise rate into a stirred and cooled (-78 °C) solution of **78.2** (44.5 mg, 0.168 mmol) in THF (10 mL) (Ar atmosphere). After 10 min, the cold bath was removed and stirring was continued for 3 h. The reaction was quenched with water (5 mL) and the mixture was partitioned between $CHCl_3$ and water. The aqueous phase was extracted twice with $CHCl_3$, and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in CH_2Cl_2 (20 mL) and 4Å molecular sieves (*ca* 100 mg) and $TsOH.H_2O$ (*ca* 15 mg) were added with stirring. Stirring was continued for 5 h, and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1.2 x 27 cm), using first hexane and then 20% EtOAc-hexane, gave **78.3** (13.8 mg, 35%) and **78.5** (20.7 mg, 48%) as oils. Compound **78.5** had: FTIR ($CHCl_3$, cast) 2976, 2953, 2918, 1715, 1636, 1476 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 3.02 (t, J = 8.7 Hz, 2 H), 3.29-3.34 (m, 4 H), 3.76-3.83 (br s, 3 H), 3.96 (dd, J = 9.4, 8.2 Hz, 2 H), 4.89 (qdd, J = 16.5, 3.7, 1.8 Hz, 2 H), 4.96-5.01 (m, 2 H), 5.81-5.93 (m, 2 H), 6.96 (d, J = 8.2 Hz, 1 H), 7.20-7.36 (br s, 0.3 H), 7.52-7.62 (br s, 0.7 H); ^{13}C NMR (CD_3OD, 100 MHz) δ 27.3 (m t), 35.6 (t), 37.5 (t), 48.7 (br t), 53.1 (br q), 113.7 (br d), 115.59 (t), 115.63 (t), 130.0 (d), 133.9 (d), 135.2 (br s), 136.7 (d), 139.1 (d); exact mass m/z calcd for $C_{16}H_{19}NO_2$ 257.14157, found 257.14105.

4-(2-Iodoethoxy)-4-methylcyclohexan-2,5-dienone (87.2).

87.1 **87.2**

$PhI(OAc)_2$ (529 mg, 1.64 mmol) and K_2CO_3 (452 mg, 3.28 mmol) were tipped into a flask which was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, 2-iodoethanol (2 mL) was injected and, after a further 5 min, a solution of freshly-distilled *p*-cresol (**87.1**) (162 mg, 1.49 mmol) in

2-iodoethanol (2 mL) was added dropwise over *ca* 5 min. A further portion of 2-iodoethanol (1 mL) was used as a rinse, which was added rapidly. Stirring was continued for 130 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between water and Et_2O, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with 1 N aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. The residue was kept under oil pump vacuum (0.4 mmHg) for 18 h in order to remove the excess of 2-iodoethanol. Flash chromatography of the residue over silica gel (24 x 1.8 cm), using 1:10:90 Et_3N-EtOAc-hexane, gave **87.2** (198.9 mg, 48%) as an oil: FTIR ($CHCl_3$, cast) 2977, 2928, 1674, 1631, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42-1.45 (m, 3 H), 3.15-3.20 (m, 2 H), 3.48-3.53 (m, 2 H), 6.24-6.29 (m, 2 H), 6.75-6.80 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.5 (t), 26.3 (q), 66.3 (t), 72.6 (s), 130.2 (d), 151.0 (d), 184.8 (s); exact mass *m/z* calcd for $C_9H_{11}IO_2$ 277.98038, found 277.98014.

7a-Methyl-2,3,3a,7a-tetrahydro-4*H*-benzofuran-5-one (87.3).

87.2 **87.3**

A solution of Bu_3SnH (0.09 mL, 0.3 mmol) and AIBN (10 mg, 0.061 mmol) in PhMe (5 mL) was added over 3 h by syringe pump into a stirred and heated (95 °C) solution of **87.2** (74.9 mg, 0.269 mmol) in PhMe (10 mL). Heating was continued for 20 min after the addition. The solvent was evaporated under water pump vacuum (the product is volatile), and flash chromatography of the residue over silica gel, using 1:10:90 Et_3N-EtOAc-hexane (and evaporation of appropriate fractions under water pump vacuum), gave **87.3** (27.3 mg, 67%) as an oil. A distilled sample (Kugelrohr oven at 120 °C, 40 mmHg)

solidified at *ca* 0 °C, but the solid melted below room temperature: FTIR (CH_2Cl_2, cast) 2970, 2878, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43 (s, 3 H), 1.69-1.78 (m, 1 H), 2.14-2.21 (m, 1 H), 2.40-2.46 (m, 1 H), 2.59 (apparent d, 4.0 Hz, 2 H), 3.76 (sextet, J = 4.5 Hz, 1 H), 3.86 (q, J = 8.0 Hz, 1 H), 5.88 (d, J = 10.2 Hz, 1 H), 6.52 (dd, J = 10.2, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.7 (q), 31.6 (t), 38.1 (t), 43.3 (d), 66.0 (t), 78.9 (s), 128.0 (d), 152.7 (d), 197.6 (s); exact mass *m/z* calcd for $C_9H_{12}O_2$ 152.08372, found 152.08378.

3-(2-Acetoxyethyl)-4-methylphenyl Acetate (87.4).

87.3 **87.4**

$TsOH.H_2O$ (5 mg, 0.03 mmol) was added into a stirred solution of **87.3** (13.9 mg, 0.0914 mmol) in a mixture of CH_2Cl_2 (2 mL) and Ac_2O (1 mL), and stirring was continued for 160 min. The flask was fitted with a condenser and then lowered into an oil bath preset at 110 °C. After 2 h, the mixture was cooled and the excess of Ac_2O was removed under oil pump vacuum. The mixture was partitioned between water and Et_2O, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using hexane-CH_2Cl_2 mixtures from 100% hexane to 100% CH_2Cl_2, gave **87.4** (14.9 mg, 69%) as an oil: FTIR ($CHCl_3$, cast) 2959, 1761, 1739, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03 (s, 3 H), 2.26 (s, 3 H), 2.29 (s, 3 H), 2.91 (t, J = 7.2 Hz, 2 H), 4.24 (t, 7.2 Hz, 2 H), 6.83-6.87 (m, 2 H), 7.13 (d, J = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.9 (q), 21.0 (q), 21.2 (q), 32.4 (t), 63.6 (t), 119.6 (d), 122.3 (d), 131.0 (d), 133.9 (s), 137.1 (s), 148.7 (s), 169.5 (s), 170.8 (s); exact mass *m/z* calcd for $C_{13}H_{16}O_4$ 236.10486, found 236.10471.

6 REFERENCES AND FOOTNOTES

1 (a) Curran, D. P.; Yu, H.; Liu, H. *Tetrahedron* **1994**, *50*, 7343. (b) Curran, D. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377.

2 (a) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119. (b) Aldabbagh, F.; Bowman, W. R. *Tetrahedron Lett.* **1997**, *38*, 3793. (c) Aldabbagh, F.; Bowman, W. R.; Mann, E. *Tetrahedron Lett.* **1997**, *38*, 7937. (d) Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991.

3 (a) Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, *63*, 2765. (b) *Cf.* Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, *58*, 3319.

4 Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 95.

5 Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747.

6 (a) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639. (b) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron Lett*, **1999**, *55*, 8111. (c) See reference 2c. (d) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett*, **2001**, *42*, 7887. (e) Escolano, C.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 8951. (f) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181. (g) Gagosz, R.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345.

7 (a) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 1795. (b) Bannasar, M.-L.; Roca, T.; Griera, R.; Bosch, J. *J. Org. Chem.* **2001**, *66*, 7547.

8 (a) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett*, **2001**, *42*, 9061. (b) Hoarau, C. Couture, A.; Cornet, H.; Deniau, D.; Grandcaudon, P. *J. Org. Chem.*

2001, *66*, 8064. (c) Harrowven, D. C.; Sutton, B. J.; Coulton, S. *Tetrahedron Lett.* **2001**, *42*, 2907.

9 (a) Marco-Contelles, J.; Rodríquez-Fernàndez, M. *Tetrahedron Lett.* **2000**, *41*, 381. (b) See reference 8c.

10 Nadin, A.; Harrison, T. *Tetrahedron Lett.* **1999**, *40*, 4073.

11 Allin, S. M.; Barton, W. R. S.; Bowman. W. R. McInally, T. *Tetrahedron Lett*, **2002**, *43*, 4191.

12 Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077.

13 Harrowven, D. C.; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett.* **2002**, *43*, 3185.

14 Harrowven, D. C; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett.* **2002**, *43*, 3189.

15 Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1994**, *50*, 2107.

16 Ellis, M. J.; Stevens, M. F. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3180.

17 Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S. *Tetrahedron* **1997**, *53*, 285.

18 (a) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S.; Pereira, A. M. D. L. *Tetrahedron* **1997**, *53*, 269. (b) Rosa, A. M.; Prabhakar, S.; Lobo, A. M. *Tetrahedron Lett.* **1990**, *13*, 1881.

19 Fiumana, A.; Jones, K. *Tetrahedron Lett.* **2000**, *41*, 4209.

20 Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765, and references therein.

21 Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977.

22 Zard, S. Z. *Angew. Chem. Int. Ed.* **1997**, *36*, 672.

23 Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 1719.

24 Liard, A.; Quinclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759.

25 (a) Ly, T.; Quinclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533. (b) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 7295.

26 Quinclet-Sire, B.; Sortais, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **2002**, 1692.

27 Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125.

28 Kaoudi, T.; Quinclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2000**, *39*, 731.

29 Beck, A. L.; Mascal, M.; Moody, C. J.; Coates, W. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 811.

30 Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

31 Citterio, A.; Fancelli, D.; Finzi, C.; Pesce, L.; Santi, R. *J. Org. Chem.* **1989**, *54*, 2713.

32 Mohan, R.; Kates, S. A.; Dombroski, M.; Snider, B. B. *Tetrahedron Lett.* **1987**, *28*, 845.

33 (a) Schmalz, H.-G.; Siegel, S.; Bats, J. W. *Angew. Chem. Int. Ed.* **1995**, *34*, 2383. (b) Kuo, C.-W.; Fang, J.-M. *Synth. Commun.* **2001**, *31*, 877. (c) Dinesh, C. U.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **1999**, *38*, 789. (d) Berndt, M.; Reissig, H.-U. *Synlett* **2001**, 1290. (e) Yang, S. M.; Nandy, A. R.; Selvakumar, A. R.; Fang, J.-M. *Org. Lett.* **2000**, *2*, 3719.

34 Tanaka, T.; Wakayama, R.; Maeda, S.; Mikamiyama, H.; Maezaki, N.; Ohno, H. *J. Chem. Soc., Chem. Commun.* **2000**, 1287.

35 Ohno, H.; Maeda, S.-I.; Okimura, M.; Wakayama, R.; Tanaka, T. *J. Chem. Soc., Chem. Commun.* **2002**, 316.

36 Clive, D. L. J.; Kang, S. *J. Org. Chem.* **2001**, *66*, 6083, and references therein.

37 Kita, Y.; Egi, M.; Takada, T.; Tohma, H. *Synthesis* **1999**, 885, and references therein.

38 Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Comm.* **1987**, 1520.

39 (a) Clive, D. L. J.; Fletcher, S. P.; Liu, D. *J. Org. Chem.* **2004**, *69*, 3282. (b) The work by Dazhan Liu reported in this paper will be submitted as part of his Doctoral Thesis.

40 (a) Pelter, A.; Ward, R. S. *Tetrahedron*, **2001**, *57*, 273. (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic: San Diego, 1997. (c) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627. (d) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523.

41 Laatsch, H. *Liebigs Ann. Chem.* **1980**, 140.

42 *Cf.* Villar, F.; Equey, O.; Renaud, P. *Org. Lett.* **2000**, *2*, 1061.

43 Otani, T.; Sugimoto, Y.; Aoyagi, Y.; Igarashi, Y.; Furumai, T.; Saito, N.; Yamada, Y.; Asao, T.; Oki, T. *J. Antibiot.* **2000**, *53*, 337.

44 Synthesis of optically pure material: Tanada, Y.; Mori, K. *Eur. J. Org. Chem.* **2001**, 4313. Synthesis of racemic material: Yang, H.; Lu, W.; Bao, J. X.; Aisa, H. A.; Cai, J. C. *Chinese Chem. Lett.* **2001**, *12*, 883; *Chem. Abstr.* **2002**, *136*, 102216.

45 Dunphy, W. G.; Kumagai, A. *Cell* **1991**, *67*, 1575.

46 Lammer, C.; Wagerer, S.; Saffrich, R.; Mertens, D.; Ansorge, W.; Hoffmann, I. *J. Cell Sci.* **1998**, *111*, 2445.

47 Bäurle, S.; Blume, T.; Günther, J.; Henschel, D.; Hillig, R. C.; Husemann, M.; Mengel, A.; Parchmann, C.; Schmid, E.; Skuballa, W. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1673.

48 Gasparotto, D.; Maestro, R.; Piccinin, S.; Vukosavljevic, T.; Barzan, L.; Sulfaro, S.; Boiocchi, M. *Cancer Res.* **1997**, *57*, 2366.

49 Galaktionov, K.; Lee, A. K.; Eckstein, J.; Draetta, G.; Meckler, J.; Loda, M.; Beach, D. *Science* **1995**, *269*, 1575.

50 Takemasa, I.; Yamamoto, H.; Sekimoto, M.; Ohue, M.; Noura, S.; Miyake, Y.; Matsumoto, T.; Aihara, T.; Tomta, N.; Tamaki, Y.; Sakita, I.; Kikkawa, N.; Matsuura, N.; Shiozaki, H.; Monden, M. *Cancer Res.* **2000**, *60*, 3043.

51 Oguri, T.; Singh, S. V.; Nemoto, K.; Lazo, J. S. *Cancer Res.* **2003**, *63*, 771 and references therein.

52 Horiguchi, T.; Nishi, K.; Hakoda, S.; Tanida, S.; Nagata, A.; Okayama, H. *Biochem. Pharmacol.* **1994**, *48*, 2139.

53 See: Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192, and references therein.

54 (a) Effenberger, F.; Burkard, U.; Willfahrt, J. *Liebigs Ann. Chem.* **1986**, 314. (b) Effenberger, R.; Burkard, U.; Willfahrt, J. *Angew. Chem. Int. Ed.* **1983**, *95*, 65.

55 1,2-Dibromoethane in combination with THF, K_2CO_3, reflux; THF, NaH, room temperature, then reflux; DMSO, NaH, room temperature, then reflux; or NaOH, EtOH, room temperature, all gave none of the desired product. A trace of desired product was observed when the starting material was treated with 1,2-dibromoethane and Cs_2CO_3 in DMF at reflux.

56 Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.

57 (a) Danishefsky, S. J.; Shair, M. D. *J. Org. Chem.* **1996**, *61*, 16. (b) Shair, M. D.; Yoon, T. Y.; Mosnie, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509. (c) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.

58 Fleck, A. E.; Hobart, J. A.; Morrow, G. W. *Synth. Commun.* **1992**, *22*, 179.

59 US Patent 2618657 (1948).

60 Klapars, A.; Huang, X.; Buchwald; S. L. *J. Am. Chem. Soc.*, **2002**, *124*, 7421.

61 German Patent 90595.

62 We thank Prof. M. McDermott (University of Alberta) for performing this experiment.

63 *Cf.* (a) Liao, C.-C. In *Modern Methodology in Organic Synthesis, Kyoto*; Sheno, T., Ed.; Kodansha: Tokyo, 1992; pp 409-424. (b) Chen, C.-H.; Rao, P. D.; Liao, C.-C. *J. Am. Chem. Soc.* **1998**, *120*, 13254. (c) Liao, C.-C.; Chu, C.-S.; Lee, T.-H.; Rao, P. D.; Ko, S.; Song, L.-D.; Shiao, H.-C. *J. Org. Chem.* **1999**, *64*, 4102. (d) Yen, C.-F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2909. (e) Hou, H.-F.; Peddinti, R. K.; Liao, C.-C. *Org. Lett.* **2002**, *4*, 2477. (f) Lin, K.-C.; Shen, Y.-L.; Roa, N. S. K.; Liao, C.-C. *J. Org. Chem.* **2002**, *67*, 8157.

64 Pouységu, L.; Avellan, A.-V.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 3425.

65 (a) Lai, C.-H.; Shen, Y.-L.; Wang, M.-N.; Rao, K.; Liao, C.-C. *J. Org. Chem.* **2002**, *67*, 6493. (b) Hong, S.-P.; McIntosh, M. C. *Org. Lett.* **2002**, *4*, 19.

66 (a) Fletcher, S. P.; Clive, D. L J.; Peng, J.; Wingert, D. A. *Submitted.* (b) The work by Jianbiao Peng reported in this paper will be submitted as part of his Doctoral Thesis.

67 Kita, Y.; Tohma, H.; Kikucho, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**. *56*, 435.

68 *Cf.* Barret, B.; Daudon, M. *Tetrahedron Lett.* **1991**, *32*, 2133.

69 *Cf.* (a) Ferraz, H. M. C.; Pereira, F. L. C.; Leite, F. S.; Nunes, M. R. S.; Payret-Arrua, M. E. *Tetrahedron* **1999**, *55*, 10915. (b) Ferraz, H. M. C.; Oliveira, E. O.; Payrat-Arrua, M. E.; Brandt, C. A. *J. Org. Chem.* **1995**, *60*, 7357.

70 (a) McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2047. (b) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K.; Yakuda, T. *J. Am. Chem. Soc.* **1992**, *114*, 2175.

71 Pelter, A.; Satchwell, P.; Ward, R. S.; Blake, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2201.

72 Ochiai, M.; Miyamoto, K.; Shiro, M.; Ozawa, T.; Yamaguchi, K. *J. Am. Chem. Soc.* **2003**, *125*, 13006.

73 (a) Ley, S. V.; Thomas, A. W.; Finch, H. *J. Chem. Soc., Perkin Trans 1*, **1999**, 669. (b) Ficht, S.; Mülbaier, M.; Giannis, A. *Tetrahedron* **2001**, *57*, 4863.

74 *Cf.* (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678. (c) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677. (d) Pelter, A.; Elgendy, M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891. (e) Lewis, N.; Wallbank, P. *Synthesis* **1987**, 1103. (f) Hara, H.; Inoue, T.; Nakamura, H.; Endoh, M.; Hoshino, O. *Tetrahedron Lett.* **1992**, *33*, 6491. (g) See reference 73a. (h) McKillop, A.; McLaren, L.; Watson, R. R.; Taylor, R. J. K.; Lewis, N. *Tetrahedron Lett.* **1993**, *34*, 5519. (i) McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. J. *J. Chem. Soc., Perkin Trans 1* **1996**, 1385. (j) Wong, Y.-S. *J. Chem. Soc., Chem. Commun.* **2002**, 686. (k) Hutinec, A.; Ziogas, A.; El-Mobayed, M.; Rieker, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2201.

75 (a) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193. (b) Braun, N. A.; Bray, J. D.; Ousmer, M.; Peters, K.; Peters, E.-M.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2000**. *65*, 4397. (c) Baxendale, I. R.; Ley, S. V.; Nessi, M.; Piutti, C. *Tetrahedron* **2002**, *58*, 6285. (d) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 4593. (e) Ousmer, M.; Bruan, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534. (f) Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411.

76 Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 1053.

77 Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* **2003**, *68*, 5429.

78 Benbow, J. W.; Katoch-Rouse, R. *J. Org. Chem.* **2001**, *66*, 4965-4972.

79 Semmelhack, M. F.; Bozell, J. J. *Tetrahedron Lett.* **1982**, *23*, 2931-2934.

GENERAL CONCLUSION

In Chapter I we reported two related syntheses of the unsubstituted core of ottelione B. Our results show that the substituents of ottelione B are not essential to stabilize the dienone substructure. The *trans* ring fused dienone **28.1**, appears to be quite robust.

In Chapter II we described a general approach to oxidative radical cyclization onto a benzene ring. The method operates under standard radical cyclization conditions and allows the formation of five-, six- and seven-membered heterocycles fused to phenols. We have developed modifications allowing construction of non-phenolic aromatic species and/or the introduction of alkyl or aryl substituents on the aromatic ring.

The method is a very effective route to benzo-fused oxygen heterocycles (Section 2.2) and gives access to substitution patterns not easily accessible by other methods. Application to the synthesis of the enantiomer of a sensitive natural product (*ent*-nocardione A) is described in Section 2.3. Our method overcomes previous limitations in the construction of substituted benzo-fused dihydrofuran rings by known methods, and a ten-fold overall yield increase was realized over Mori's prior synthesis of optically pure nocardione A.

The synthetic work in Section 2.3 involves the development of a flexible and general route to a wide range of benzo-fused nitrogen heterocycles. A general method to such structures is currently not available. The results in this section also significantly expand what was known about the oxidation of *p*-aminophenols.